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(54) **N-Heterocyclyl-4-piperidinamines, methods for their preparation, pharmaceutical compositions comprising them, intermediates therefor, and method for the preparation of the intermediates.**

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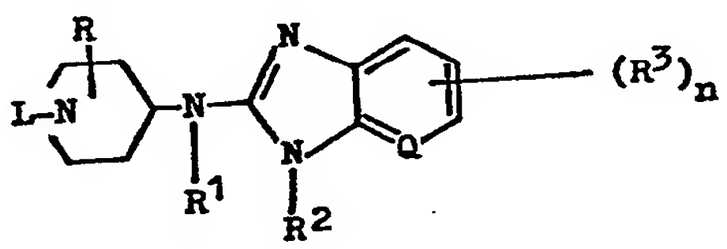
N-Heterocyclyl-4-piperidinamines, methods for their preparation, pharmaceutical compositions comprising them, intermediates therefor, and method for the preparation of the intermediates

BACKGROUND OF THE INVENTION

In U.S. Pat. No. 2,971,005 there are described 2-(phenylmethylamino)benzimidazoles having local anaesthetic and antifibrillatory properties and in U.S. Pat. No. 2,857,391 there are described a number of 2-(aminomethyl)benzimidazoles. The compounds of this invention differ therefrom essentially by the nature of the 4-piperidinyl-group, attached to the amino nitrogen atom and by their unexpected antihistaminic properties. Also known in the art is 1-methyl-N-phenyl-N-phenylmethyl-4-piperidinamine, an antihistaminic compound which is generically designated as Bamipine (see the Merck index, 8th edition (1968) p. 118). The compounds of this invention are structurally different since they invariably contain a 1H-benzimidazol-2-yl or 3H-imidazo[4,5-b]pyridin-2-yl radical, attached to the amino nitrogen atom.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention is concerned with a novel series of N-heterocyclyl-4-piperidinamines which may structurally be represented by the formula:



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and lower alkyl;

R^1 is a member selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryllower alkyl and lower alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, cycloalkyl and mono- and diaryl(lower alkyl);

R^3 is a member independently selected from the group consisting of halo, lower alkyl lower alkyloxy and trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of lower alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, lower alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; lower alkenyl; arryllower alkenyl; cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryllower alkyl)-1H-benzimidazol-2-yl; and a radical of the formula $Z—C_mH_{2m}—$, wherein

m is an integer of from 1 to 6 inclusive; and

Z is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a lower alkyl radical 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cycloheptен-5-ylidene)methyl- 4-morpholinyl; 1 piperidinyl; 1-pyrrolidinyl; a radical of the formula $T—N(R^4)—$, wherein

R^4 is a member selected from the group consisting of hydrogen, lower alkyl and aryllower alkyl; and

T is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula

$$W—\overset{\overset{O}{\|}}{C}—(X)_s—$$, wherein

s is the integer 0 or 1;

X is a member selected from the group consisting of O and $—N(R^5)—$, said R^5 being a member selected from the group consisting of hydrogen, lower alkyl, aryllower alkyl, lower alkanoyl and aroyl; and

W is a member selected from the group consisting of lower alkyl, aryl, aryllower alkyl, amino, arylamino mono- and di(lower alkyl)amino, mono- and di(aryllower alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (lower alkyl)thienyl, pyridinyl, mono-

and di-(lower alkyloxy)pyridinyl, furanyl and 1-(lower alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, lower alkyl, lower alkylthio, lower alkylsulfonyl, lower alkylsulfonyllower alkyl, phenyllower alkylsulfonyl, phenylsulfonyllower alkyl, amino, mono- and di(lower alkyl)amino, lower alkanoyl, a radical of the formula $R^6—C_pH_{2p}—O—$, wherein

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(lower alkyl)aminocarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, lower alkenyl; and

a radical of the formula $R^7—O—$, wherein

R^7 is a member selected from the group consisting of alkanoyl, phenylcarbonyl, phenyllower alkylcarbonyl, lower alkyloxycarbonyl, phenyllower alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di(lower alkyl)aminocarbonyl;

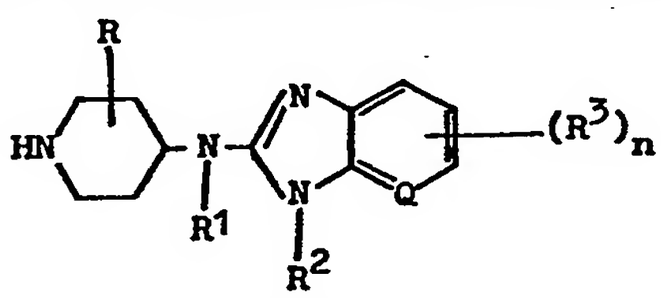
wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, lower alkyl and lower alkyloxy; and

wherein said aroyl in the definition of said L represents arylcarbonyl

wherein said aryl is as defined hereabove.

As used in the foregoing definitions the term "lower alkyl" is meant to include straight and branch chained hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; the term "alkyl" as used in the definition of R^2 includes straight and branch chained hydrocarbon radicals having from 1 to 10 carbon atoms, such as, for example, the above-indicated lower alkyls and higher homologs such as heptyl, octyl, nonyl and decyl; the term "lower alkenyl" refers to straight alkenyl radicals having from 3 to 6 carbon atoms wherein the unsaturation is preferably located at the β-position but may also be located at the γ, δ, or ε-position such as for example, 2-propenyl, 2-butenyl, 3-pentenyl, 2-hexenyl and the like; the term "cycloalkyl" refers to cyclic hydrocarbon radicals having from 3 to 6 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the term "halo" is generic to fluoro, chloro, bromo and iodo.

The compounds of formula (I) can generally be derived from a starting material of the formula



(II)

wherein R, R^1, R^2, R^3, n and Q are as previously defined by introducing the desired L-substituent onto the piperidine nitrogen by the application of art-known methods.

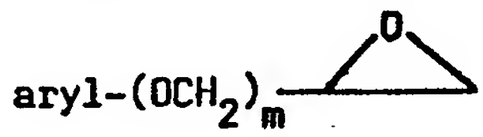
In general the introduction of said L into the intermediate (II) may conveniently be accomplished by the reaction of (II) with an appropriate reactive ester of the formula LY, (III), wherein L is as previously defined and Y is a reactive ester residue such as, for example, halo, preferably chloro or bromo, or a sulfonyloxy residue such as, for example, methylsulfonyloxy or 4-methylphenylsulfonyloxy and the like.

The condensation reaction of (II) with (III) is conveniently conducted in an inert organic solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, methylbenzene, dimethylbenzene, and the like; a lower alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane and the like; N,N-dimethylformamide (DMF): nitrobenzene; and the like.

The addition of an appropriate base such as, for example, an alkali metal carbonate or hydrogen carbonate, or an organic base such as, for example, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be utilized to pick up the acid that is liberated during the course of the reaction. In some circumstances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures may be employed to enhance the rate of the reaction.

When L in formula (I) represents a (2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)lower alkyl radical it is appropriate to use a reactive ester (III) wherein the nitrogen atom in the 3-position of the 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl group is substituted with an appropriate protecting group, preferably a 1-methylethenyl group and removing said protecting group after completion of the condensation reaction. The removal of said protecting group may be accomplished by art-known procedures, such as acid hydrolysis when a 1-methylethenyl group is involved.

When L represents a 2-aryl-2-hydroxyethyl or a 2-aryloxy 2-hydroxypropyl radical, the introduction of said substituent into the intermediate (II) may conveniently be carried out by reacting (II) at an elevated temperature with an appropriate oxirane of the formula



(IV)

wherein m is 0 or 1.

The reaction of (II) with (IV) may be carried out in an appropriate organic solvent or, optionally, in the absence of any solvent. Suitable solvents which may be employed include, for example aromatic hydrocarbons such as benzene, methylbenzene, dimethylbenzene and the like; halogenated hydrocarbons such as, for example, trichloromethane, dichloromethane and the like; lower alkanols such as, methanol, ethanol, 2-propanol and the like alcohols; and mixtures of such solvents. When the piperidine derivative (II) is in the form of an acid addition salt it is appropriate to add to the reaction mixture an appropriate base such as, for example, sodium carbonate in order to liberate the free acid from the salt.

The compounds of formula (I) wherein L represents a 2-hydroxyethyl radical may be prepared by the reaction of an appropriate piperidine of formula (II) with oxirane, following the same procedure as described for the reaction of (IV) with (II).

When L is, at the point of attachment to the piperidine nitrogen atom, a primary or secondary alkyl group, the compounds (I) may also be prepared by the reductive amination of an aldehyde or ketone corresponding with the alcohol L—OH with a piperidine derivative of formula (II) following art-known procedures.

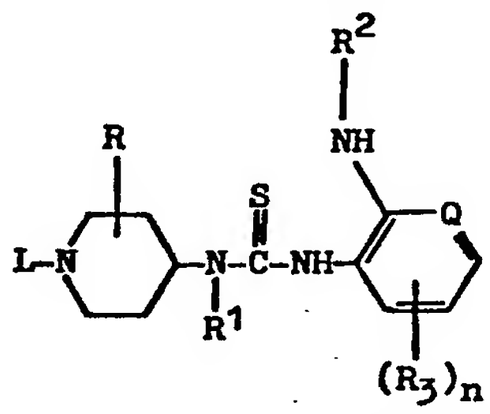
In a convenient method of operation a mixture of the aldehyde or ketone and (II) in an appropriate organic solvent is hydrogenated in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal.

Appropriate organic solvents include lower alkanols, such as, for example, methanol, ethanol, propanol and the like. The rate of the hydrogenation reaction may be enhanced by carrying out said reaction in the presence of an appropriate weak acid such as, for example, acetic acid. When the piperidine derivative (II) is in the form of an addition salt with a strong acid, e.g., hydrochloric or hydrobromic acid it is appropriate to add thereto a salt of a strong base with a weak acid, e.g., sodium acetate to bind said strong acid. When (II) contains groups that are themselves susceptable to catalytic hydrogenation, e.g. when R^2 represents an arylmethyl group, it may be appropriate to add to the reaction mixture an appropriate catalyst poison such as, for example, thiophene.

When L represents a radical of formula Z—C_mH_{2m}—, wherein m is an integer of from 2 to 6 inclusive and wherein Z is as previously defined, the compounds of formula (I) can also be prepared by the reaction of (II) with an appropriate alkenyl derivative, Z—C_mH_{2m-1}, according to art-known methods of carrying out similar addition-reactions, e.g., by stirring and heating the reactants together in and appropriate reaction-inert organic solvent such as, for example a lower alkanol such as 2-propanol, butanol and the like.

When L represents a 2-(aroylamino)ethyl radical or a 2-aryl-ethyl radical the compounds (I) can also be obtained by the reaction of (II) with an appropriate 1-aroylaziridine or an appropriate ethenylarene, respectively. Said reactions are preferably carried out in an appropriate reaction-inert organic solvent, such as, for example, a lower alkanol, e.g. methanol, ethanol, propanol, butanol and the like alcohols; an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; a ketone, e.g., 4-methyl-2-pentanone; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane and the like; N,N-dimethylformamide; nitrobenzene; and the like; or a mixture of such solvents. Elevated temperatures are appropriate in order to enhance the rate of the reaction and preferably the reaction is carried out at the reflux temperature of the reaction mixture.

The compounds of formula (I) can also be prepared by the cyclodesulfurization of an appropriate thiourea derivative of the formula



(V)

Said cyclodesulfurization reaction may be carried out by the reaction of (V) with an appropriate alkyl halide, preferably iodomethane in an appropriate reaction-inert organic solvent, e.g., a lower alkanol such as methanol, ethanol, 2-propanol and the like. Otherwise, the cyclodesulfurization reaction may be carried out by the reaction of (V) with an appropriate metal oxide or salt in an appropriate solvent according to the procedure described, for example, in Pharmazie, *31*, 348 (1976). For example, the

compounds of formula (I) can easily be prepared by the reaction of (V) with an appropriate Hg(II) or Pb(II) oxide or salt, such as, for example HgO, $HgCl_2$, $Hg(OAc)_2$, PbO or $Pb(OAc)_2$. In certain instances it may be appropriate to supplement the reaction mixture with a small amount of sulfur. Even so methanediimines, especially N,N′-methanetetraylbis[cyclohexanamine], may be used as cyclo-desulfurizing agents.

Suitable reaction-inert organic solvents that may advantageously be employed include lower alkanols, e.g., methanol, ethanol, 2-propanol and the like; halogenated hydrocarbons, e.g., dichloromethane and trichloromethane; ethers, e.g. tetrahydrofuran, 2,2′-oxybispropane and the like; and mixture of such solvents.

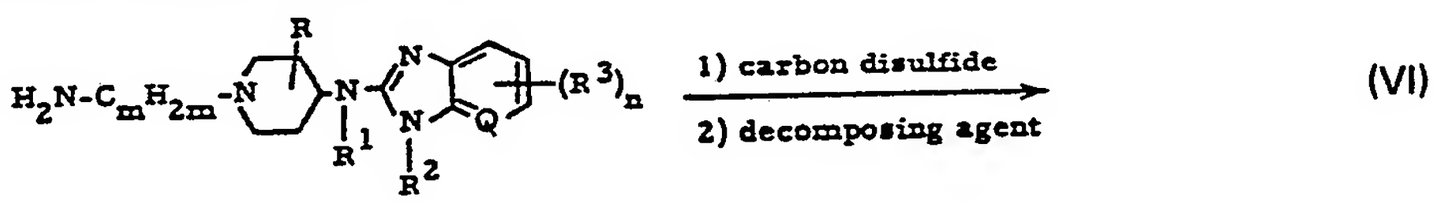
The compounds of formula (I) wherein R^2 is other than hydrogen, said R^2 being represented by R^2_a and said compounds by the formula (I-a), can also be prepared starting from a corresponding compound (I) wherein R^2 is hydrogen, (I-b), by introducing said R^2_a according to art-known procedures as previously described herein for the introduction of L into starting materials of formula (II). In a preferred method of operation (I-b) is reacted with an appropriate reactive ester R^2_aY, (VI), wherein R^2_a and Y are as previously defined. The reaction is carried out under similar conditions as previously described herein for the reaction of (II) with (III). Since the compounds of formula (I-b) are somewhat less reactive it is advantageous to conduct the alkylation reaction in the presence of a small amount of a strong metal base such as, for example, sodium hydride.

The compounds of formula (I) wherein R^1 and R^2 are both different from hydrogen, said R^1 being represented by R^1_a and said R^2 by R^2_a can also be derived from the corresponding compounds wherein R^1 is hydrogen by introduicng the R^1_a-group in a similar manner as described hereinabove for the preparation of compound (I-b) starting from (I-a).

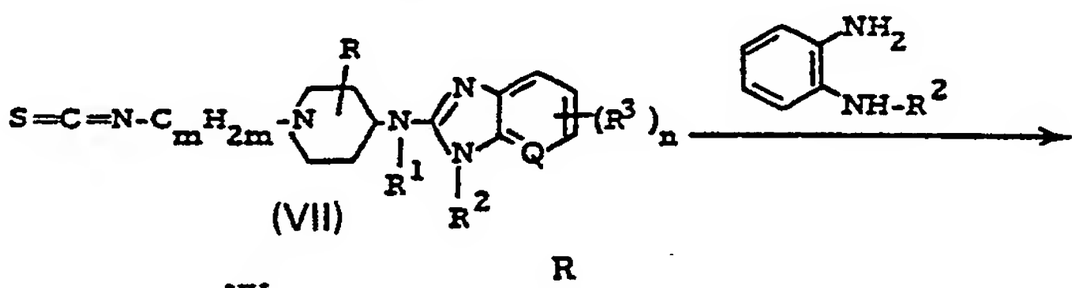
Following the procedure, described hereinabove for the preparation of compounds (I) starting from (V), the compounds of formula (I), wherein L represents a (1H-benzimidazol-2-ylamino) lower alkyl radical or a 1-(aryllower alkyl)-1H-benzimidazol-2-ylamino)lower alkyl radical (I-c), may even so be derived from the corresponding isothiocyanates (VII) by subjecting the latter to an addition-reaction with a benzenediamine (VIII) and subsequently cyclodesulfurizing the intermediately formed thiourea (IX).

The isothiocyanates (VII) may be prepared following art-known procedures for the preparation of isothiocyanates [see, for example, Saul Patai Ed. "The Chemistry of Cyanates and their Thio-derivatives" John Wiley & Sons — Chichester — New York — Brisbane — Toronto (1977) p. 1013—1053], such as, for example by reacting the corresponding amine (VI) with carbon disulfide, preferably in the presence of alkali e.g., sodium hydroxide and the like, and decomposing the intermediately formed dithiocarbamate with for example N,N′-methanetetraylbis [cyclohexanamine], a lower alkyl chloroformate or another appropriate decomposing agent as known in the art.

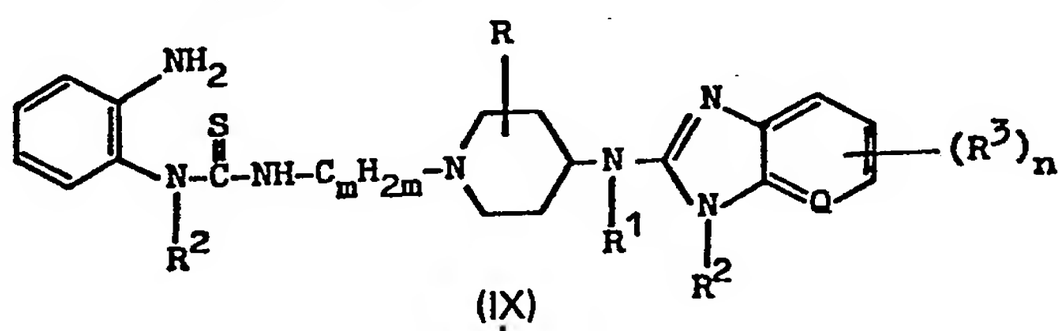
The foregoing reactions are illustrated as follows:



(VI)

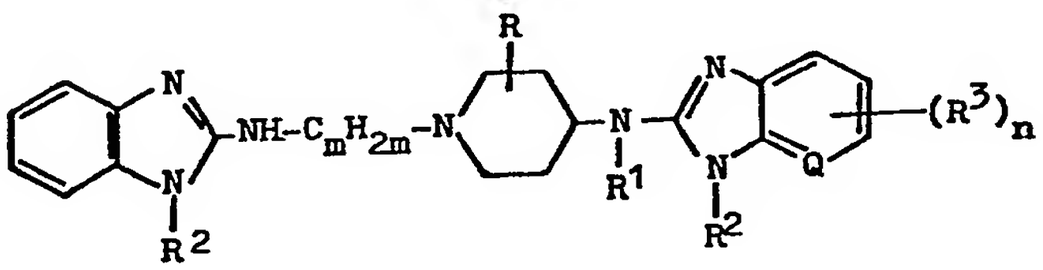


(VII) (VIII)



(IX)

cyclodesulfurization



(I-c)

The compounds of formula (I) wherein L represents a radical Z—C_mH_{2m}—, wherein Z represents a radical of the formula W—CO—$(X)_s$—, wherein s is 1, X is O and W is an optionally substituted amine, a 1-pyrrolidinyl, a 4-morpholinyl or a 1-piperidinyl radical, said compounds being represented by the formula (I-d), may be prepared by the reaction of the corresponding amine, pyrrolidine, morpholine or piperidine with an appropriate N-[1-(halolower alkyl)-4-piperidinyl]-1H-benzimidazol-2-amine in the presence of an appropriate carbonate, e.g. sodium carbonate and the like.

Compounds of formula (I) which contain at least one hydroxyl-group as a substituent can conveniently be derived from the corresponding phenylmethoxy substituted compounds by subjecting the latter to a catalytic hydrogenation in the presence of an appropriate catalyst, e.g., palladium-on-charcoal and the like. These hydroxyl-derivatives may even so be derived from the corresponding lower alkyloxy substituted analogs by hydrolyzing the latter in acidic medium, using for example hydrogen bromide in acetic acid.

The hydroxyl-substituted compounds may in turn be O-alkylated or acylated by reacting the latter with a halide, an alkanoyl halide, an alkyloxycarbonyl halide, an isocyanate and the like.

The hydroxyl-substituted compounds may also be converted into halides by reacting therewith a suitable halogenating agent, e.g. thionyl chloride, phosphor pentabromide and the like in the presence of an appropriate solvent, e.g., a trichloromethane and the like.

Amino-substituted compounds may, for example be derived from the corresponding nitro- and cyano-substituted compounds by reducing the latter, e.g., by catalytic hydrogenation in the presence of an appropriate catalyst, such as, for example, Raney-nickel and the like.

The amino-substituted compounds may in turn be N-alkylated or acylated by the reaction thereof with an appropriate alkylating agent or acylating agent, e.g., a halide, an alkanoyl halide, an alkoxycarbonyl halide, an isocyanate and the like.

Secondary and tertiary amino-substituted compounds of formula (I) may be prepared by substituting, for example, an appropriate halo-substituted compound with the desired primary or secondary amine.

Aminocarbonyl-substituted compounds may conveniently be derived from the corresponding esters by reacting the latter with ammonia or an appropriate primary-or a secondary amine in a suitable solvent.

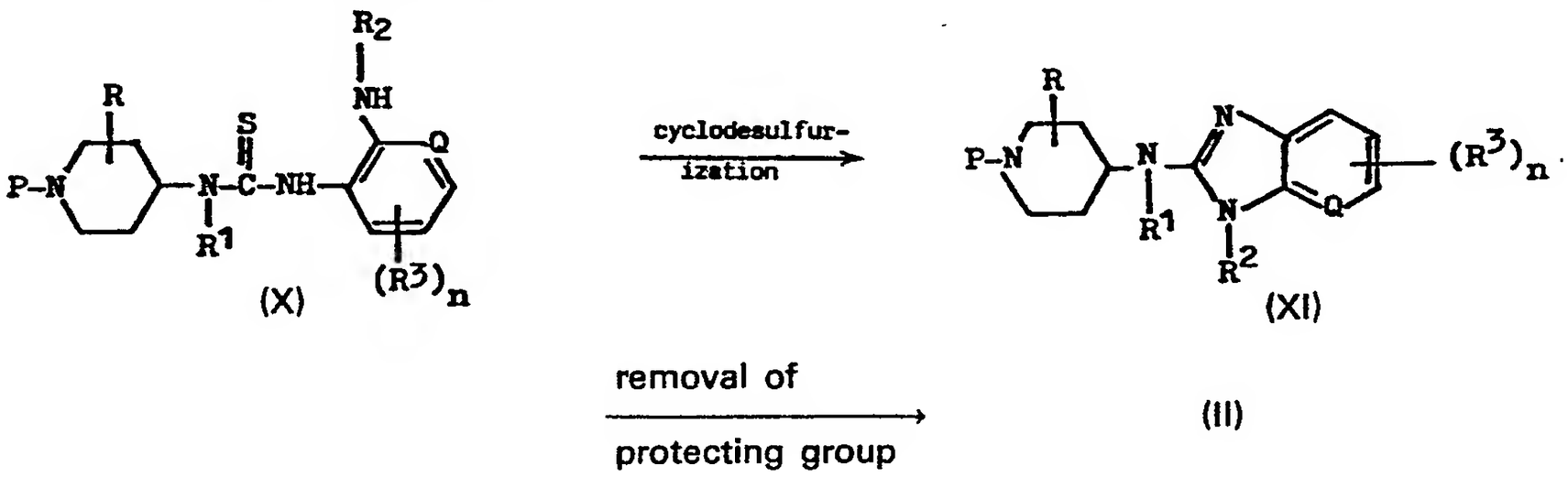
Compounds of formula (I) which contain in their structure a sulfonyl group may easily be derived from the corresponding thio compounds by oxidizing the latter with an appropriate oxydizing agent, e.g. hydrogen peroxide and the like.

In all of the foregoing and in the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

The compounds of formula (I) may be converted to the therapeutically active non-toxic acid addition salt form by treatment with an appropriate acid, such as, for example, an inorganic acid, such as hydrohalic acid, e.g., hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or an organic acid, such as, for example, acetic, propanoic, 2-hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, benzoic, 3-phenyl-2-propenoic, α-hydroxybenzeneacetic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

Conversely the salt form can be converted by treatment with alkali into the free base form.

The starting materials of formula (II) herein can generally be prepared starting from a thiourea derivative of the formula (X) wherein R, R^1, r^2, R^3 and n are as previously defined and P is an appropriate protecting group such as, for example, lower alkyloxycarbonyl or phenylmethoxycarbonyl, by subjecting (X) to a cyclodesulfurization reaction to obtain an intermediate of the formula (XI) and thereafter eliminating the protecting group in the usual manner.

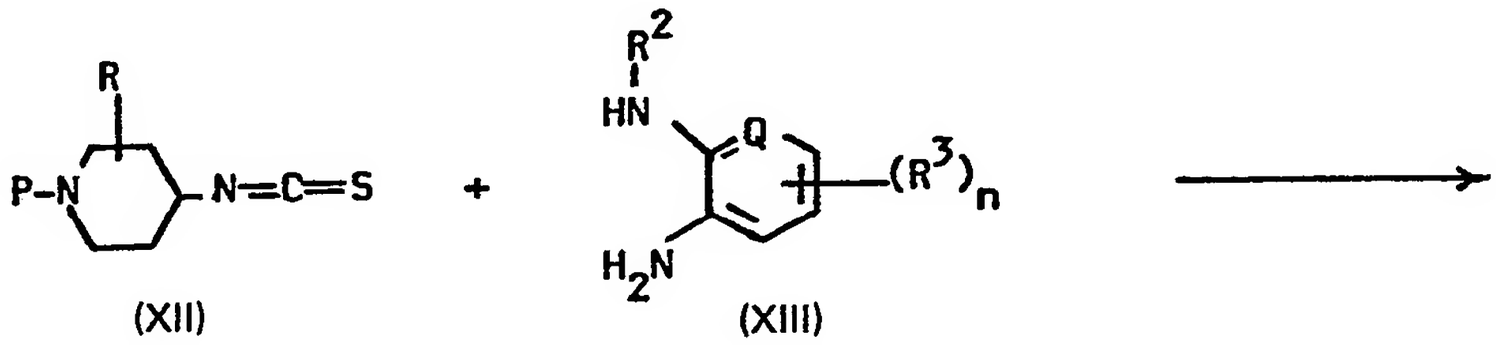


The cyclodesulfurization of (X) to obtain (XI) can be carried out in the same manner as previously

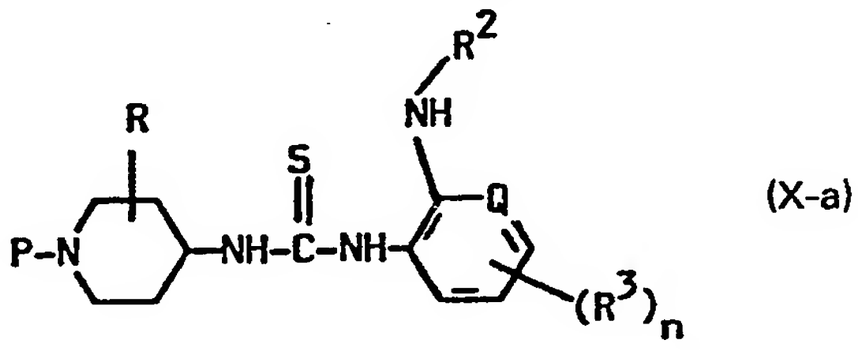
described herein for the preparation of the compounds (I) starting from (V). In order to remove the protecting group P there may be used art-known procedures. For example, when said group is a lower alkyloxycarbonyl group it may be removed by alkaline or preferably acid hydrolysis, using for example, hydrobromic acid in glacial acetic acid, and when said protecting group is a phenylmethoxycarbonyl group it may be removed by alkaline or acid hydrolysis or by catalytic hydrogenation using an appropriate catalyst such as palladium-on-charcoal.

Intermediates of formula (XI) wherein R^2 is other than hydrogen can also be derived from the corresponding (XI) wherein R_2 is hydrogen by introducing the desired R^2-substituent according to art-known methodologies as described hereinabove in connection with the preparation of compounds (I-a) starting form (I-b).

The thiourea derivatives of formula (X) wherein R^1 represents hydrogen, (X-a), can be prepared by the reaction of an appropriate 4-isothiocyanatopiperidine of formula (XII) with an appropriate benzenediamine or pyridinediamine of formula (XIII), e.g. by simply stirring the reactants together in an appropriate organic solvent such as, for example, a lower alkanol, e.g. methanol, ethanol, 2-propanol and the like.

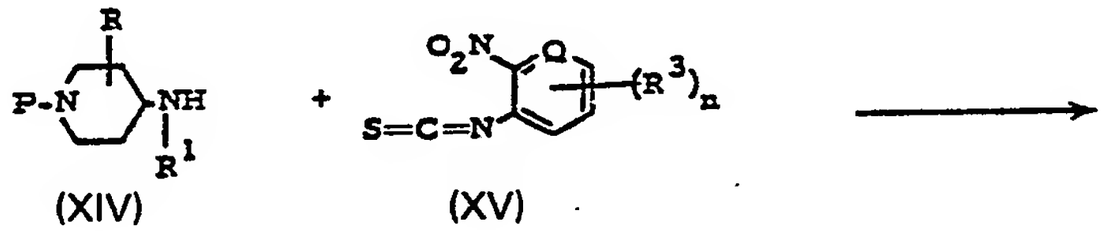


(XII) (XIII)

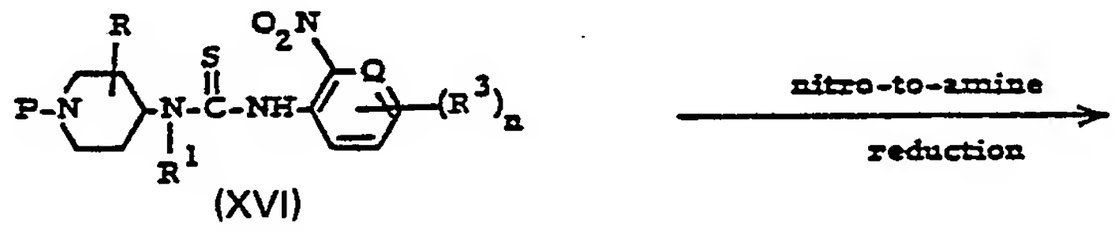


(X-a)

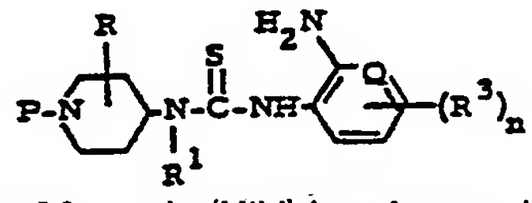
Thiourea derivatives of formula (X) wherein R^1 is as previously defined and R^2 is hydrogen, (X-b), can be prepared by the reaction of an appropriate 4-piperidinamine of the formula (XIV) with an appropriate 1-isothiocyanato-2-nitrobenzene of the formula (XV), followed by the reduction of the nitro group of the thus obtained compound (XVI) following well-known nitro-to-amine reduction procedures such as for example by the reaction of (XVI) with nascent hydrogen or by catalytic hydrogenation using an appropriate catalyst such as, for example, palladium-on-charcoal, platinium-on-charcoal and the like, or in the presence of more than one of such catalysts.



(XIV) (XV)



(XVI)



(X-b)

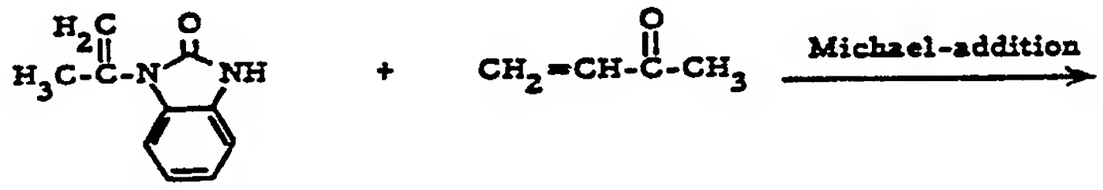
The precursor materials of formula (XIV) herein may be prepared following methods known in the art, e.g., by the reductive amination of the corresponding 4-piperidinone. The 4-isothiocyanato-piperidines of formula (XII) may in turn be prepared starting from the corresponding (XIV) wherein R^1 is hydrogen according to standard methods of preparing isothiocyanates starting from primary amines, e.g., by the reaction of the amine with carbon disulfide in alkaline medium and subsequent addition to the reaction mixture of an appropriate lower alkylcarbonochloridate.

The starting materials of formula (XII) wherein P represents a lower alkyloxycarbonyl or phenylmethoxycarbonyl group can also be prepared by the reaction of a corresponding starting material (XII) wherein said P represents phenylmethyl by reacting the latter with an appropriate carbonochloridate.

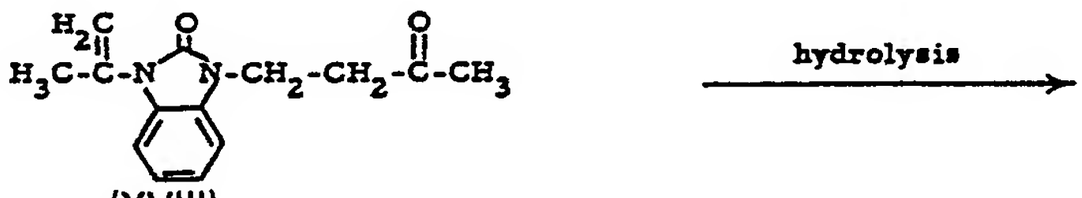
The starting materials of formula (V) can be prepared using similar procedures as described hereinabove for the preparation of the thiourea derivatives of formula (X) starting however from an appropriate 4-piperidinone or 4-piperidinamine wherein the L-substituent is already present on the piperidine nitrogen atom.

The ultimate starting materials in each of the foregoing preparations are known compounds or they may be prepared by the application of methodologies known in the art for preparing similar known compounds.

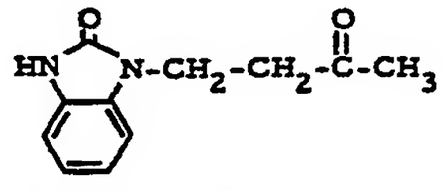
The preparation of 4-(haloalkyl)-2H-1,4-benzoxazin-3(4H)-ones, for example, by the N-substitution-reaction of 2H-1,4-benzoxazin-3(4H)-one with a dihalolower alkyl group, is described in Belg. Pat. No. 859,415. 1,3-dihydro-1-(3-oxobutyl)-2H-benzimidazol-2-one (XIX) can be prepared by subjecting 1,3-dihydro-1-(1-methylethenyl)-2H-benzimidazol-2-one (XVII) and 3-buten-2-one to a Michael-addition procedure in the presence of a base such as, N,N-diethylethanamine and the like, and subsequently hydrolyzing the 1,3-dihydro-1-(1-methylethenyl)-3-(3-oxobutyl)-2H-benzimidazol-2-one (XVIII).



(XVII)



(XVIII)



(XIX)

The intermediates of the formulae (II) and (XI) are deemed to be novel and in view of their utility as starting materials in the preparation of the pharmaceutically active compounds of formula (I) they constitute an additional feature of this invention.

The compounds of formula (I) and their pharmaceutically acceptable acid addition salts are potent antihistaminic agents and as such they can be used to prepare valuable medicaments for human and animal therapy.

The useful antihistaminic properties of the compounds of formula (I) were demonstrated in the following test procedure.

Protection of rats from compound 48/80 — induced lethality.

Compound 48/80, a mixture of oligomers obtained by condensation of p-methoxy-N-methylphenylamine and formaldehyde has been described as a potent histamine releasing agent (Int. Arch. Allergy, *13*, 336 (1958)). The protection from compound 48/80-induced lethal circulatory collapse appears to be a simple way of evaluating quantitatively the antihistaminic activity of test-compounds. Male rats of an inbred Wistar strain, weighing 240—260 g were used in the experiment. After overnight starvation the rats were transferred to conditioned laboratories (temp. = 21 ± 1°C, relative humidity = 65 ± 5%).

The rats were treated subcutaneously or orally with a test compound or with the solvent (NaCl solution, 0.9%). One hour after treatment there was injected intravenously compound 48/80, freshly dissolved in water, at a dose of 0.5 mg/kg (0.2 ml/100 g of body weight).

In control experiments, wherein 250 solvent-treated animals were injected with the standard dose of compound 48/80 not more than 2.8% of the animals survived after 4 hours. Survival after 4 hours is therefore considered to be a safe criterion of a protective effect of drug administration.

The compounds of formula (I) and the pharmaceutically acceptable acid addition salts thereof were found very active in the above test, protecting the animals against compound 48/80-induced lethality at oral and subcutaneous doses not higher than 2.5 mg/kg. A number of the subject compounds were found effective even at doses as low as 0.16 mg/kg.

In view of their useful antihistaminic activity, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, an effective antihistaminic amount of the particular compound, in base or acid-

addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Acid additions salt of (I), due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The following examples are intended to illustrate and not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

A. Preparation of intermediates:

Example I

A mixture of 102 parts of ethyl 4-oxo-1-piperidinecarboxylate, 50 parts of methanamine and 400 parts of methanol is hydrogenated at normal pressure and at room temperature with 5 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated, yielding 111 parts of ethyl 4-(methylamino)-1-piperidine-carboxylate as a residue.

To a stirred and cooled mixture of 4 parts of sodium hydroxide in 60 parts of water are added successively 7.9 parts of carbon disulfide and 17.2 parts of ethyl 4-amino-1-piperidinecarboxylate at a temperature below 10°C. Stirring is continued for 30 minutes at this temperature. Then there are added dropwise 10.9 parts of ethyl carbonochloridate (exothermic reaction: temp. rises to about 35°C). Upon completion, stirring is continued for 2 hours at 60°C. The reaction mixture is cooled and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated, yielding 22 parts (100%) of ethyl 4-isothiocyanato-1-piperidinecarboxylate as a residue.

By repeating the procedure of the second step there are also prepared starting from an appropriate amine:

4-isothiocyanato-1-(phenylmethyl)piperidine; and
1-[4,4-bis)4-fluorophenyl)butyl]-4-isothiocyanatopiperidine; mp. 92°C.

Example II

To a stirred solution of 28.4 parts of 4-isothiocyanato-1-(phenylmethyl)piperidine in 315 parts of methylbenzene are added dropwise 41 parts of (phenylmethyl) carbonochloridate at room temperature. Upon completion, the whole is heated to reflux and stirring is continued overnight at reflux temperature. The reacton mixture is cooled and the solvent is evaporated. The residue is purified by column-chromatography over silica gel using trichloromethane as eluent. The pure fractions are collected and the eluent is evaporated, yielding 32 parts (97%) of (phenylmethyl) 4-isothio-cyanato-1-piperidinecarboxylate as a residue.

Example III

A mixture of 9.7 parts of 4-fluorobenzenemethanamine hydrochloride, 9.4 parts of 2-chloro-3-nitropyridine, 10.6 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred for 1 hour at 90°C. The reaction mixture is cooled and poured onto water. The precipitated product is filtered off and crystallized from 2-propanol, yielding 10.5 parts (71%) of N-(4-fluorophenylmethyl)-3-nitro-2-pyridinamine; mp. 76°C.

A mixture of 10.5 parts of N-(4-fluorophenylmethyl)-3-nitro-2-pyridinamine and 200 parts of methanol is hydrogenated at normal pressure and at room temperature with 2 parts of Raney-nickel

catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated, yielding 9.3 parts (100%) of N^2-(4-fluorophenylmethyl)-2,3-pyridinediamine as a residue.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

N^1(phenylmethyl)-4-(trifluoromethyl)-1,2-benzenediamine; and
4-chloro-N^1-(4-fluorophenylmethyl)-1,2-benzenediamine.

Example IV

A mixture of 34.8 parts of 1,3-dihydro-1-(1-methylethenyl)-2H-benzimidazol-2-one, 28 parts of 3-buten-2-one, 20.2 parts of N,N-diethylethanamine and 270 parts of tetrahydrofuran is stirred and refluxed over week-end. The reaction mixture is evaporated, yielding 48.8 parts (100%) of 1,3-dihydro-1-(1-methylethenyl)-3-(3-oxobutyl)-2H-benzimidazol-2-one as a residue.

A mixture of 48.8 parts of 1,3-dihydro-1-(1-methylethenyl)-3-(3-oxobutyl)-2H-benzimidazol-2-one, 12 parts of 2-propanol, saturated with gaseous hydrogen chloride and 240 parts of 2-propanol is stirred for 3 hours at room temperature. The precipitated product is filtered off, washed with 2,2'-oxybispropane and dried, yielding 30 parts (73.4%) of 1,3-dihydro-1-(3-oxobutyl)-2H-benzimidazol-2-one.

Example V

To a stirred mixture of 9 parts of 2H-1,4-benzoxazin-3(4H)-one, 0.9 parts of N,N,N-triethylbenzenemethanaminium chloride, 9 parts of sodium hydroxide solution 50% and 24 parts of water are added 10.4 parts of 1-bromo-3-chloropropane at 30°C. The whole is heated to 90°C and stirring is continued for 3 hours at this temperature. The reaction mixture is cooled to about 70°C, methylbenzene is added and the whole is stirred overnight at room temperature. The organic phase is separated, dried, filtered and evaporated, yielding 10 parts of 4-(3-chloropropyl)-2H-1,4-benzoxazin-3(4H)-one as a residue.

Example VI

A mixture of 10.6 parts of ethyl 4-isothiocyanato-1-piperidinecarboxylate, 11.6 parts of 4-chloro-N^1-(phenylmethyl)-1,2-benezenediamine and 90 parts of tetrahydrofuran is stirred overnight at room temperature. The reaction mixture is evaporated, yielding 21 parts (100%) of ethyl 4 - [{[{5 - chloro - 2 - [(phenylmethyl)amino]phenyl}amino]thioxomethyl}amino] - 1 - piperidinecarboxylate; mp. 162°C.

Example VII

Following the procedure of Example VI and using equivalent amounts of the appropriate starting materials there are prepared:

ethyl 4 - {[(2 - amino - 5 - chlorophenyl)aminothioxomethyl]amino} - 1 - piperidinecarboxylate; mp. 162.2°C;
ethyl 4 - {[(2 - aminophenyl)aminothioxomethyl]amino} - 1 - piperidinecarboxylate as a residue:
ethyl 4 - {[(2 - amino - 5 - methylphenyl)aminothioxomethyl]amino} - 1 - piperidinecarboxylate as a residue;
ethyl 4 - [{[{2 - [(phenylmethyl)amino] - 3 - pyridinyl}amino]thioxomethyl}amino] - 1 - piperidinecarboxylate; mp. 146.7°C;
ethyl 4 - {[{2 - [(phenylmethyl)amino] - 5 - (trifluoromethyl)phenyl}amino]thioxomethylamino} - 1 - piperidinecarboxylate as a residue;
ethyl 4 - [{[(2 - amino - 4 - fluorophenyl)amino]thioxomethyl}amino] - 1 - piperidinecarboxylate as a residue;
ethyl 4 - [{[{5 - chloro - 2 - [(4 - fluorophenylmethyl)amino]phenyl}amino]thioxomethyl}amino] - 1 - piperidinecarboxylate as a residue;
(phenylmethyl) - 4 - [{2 - [(4 - fluorophenylmethyl)amino] - 3 - pyridinylamino}thioxomethylamino] - 1 - piperidinecarboxylate;
N - (2 - nitrophenyl) - N' - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N' - (phenylmethyl)thiourea; mp. 151.1°C;
N - {1 - [4,4 - bis(4 - fluorophenyl)butyl] - 4 - piperidinyl} - N' - phenylthiourea; mp. 90°C;
ethyl 4 - [{[(2 - amino - 3 - pyridinyl)amino]thioxomethyl}amino] - 1 - piperidinecarboxylate; m.p. 176.9°C;
4 - [{[(2 - phenylamino)phenyl]aminothioxomethyl}amino] - 1 - piperidinecarboxylate; mp. 154.2°C; and
ethyl 4 - {[{[2 - (4 - fluorophenylamino)phenyl]amino}thioxomethyl]amino} - 1 - piperidinecarboxylate as a residue.

Example VIII

A mixture of 21.6 parts of 1-isothiocyanato-2-nitrobenzene and 45 parts of tetrahydrofuran is stirred till all solid enters solution. Then there are added 29.5 parts of N-(1-methylethyl)-1-(2-phenylethyl)-4-piperidinamine and 160 parts of ethanol and the whole is stirred overnight at room tempera-

ture. The reaction mixture is evaporated and the residue is crystallized from 2-propanol. The product is filtered off and dried, yielding 43 parts (84%) of N-(1-methylethyl)-N′-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]thiourea; mp. 100.6°C.

Example IX

Following the procedure of Example VIII the following thiourea derivatives are prepared by the reaction of an appropriate 4-piperidinamine with an appropriate 1-isothiocyanato-2-nitrobenzene.

ethyl 4-[methyl-{[(2-nitrophenyl)amino]thioxomethyl}amino]-1-piperidinecarboxylate;
ethyl 4-{butyl[(2-nitrophenyl)aminothioxomethyl]amino}-1-piperidinecarboxylate as a residue;
N-ethyl-N′-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]thiourea;
N-(2-nitrophenyl)-N′-[1-(2-phenylethyl)-4-piperidinyl]-N′-propylthiourea; mp. 90.3°C;
N-cyclopropyl-N′-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]thiourea; mp. 150.1°C; and
cis+*trans*-methyl 3-methyl-4-[{[(2-nitrophenyl)amino]thioxomethyl}amino]-1-piperidinecarboxylate; mp. 157.5°C.

Example X

A mixture of 43 parts of N-(1-methylethyl)-N′-(2-nitrophenyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-thiourea and 800 parts of methanol, saturated with ammonia is hydrogenated at normal pressure and at room temperature with 6 parts of palladium-on-charcoal catalyst 10% and 6 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen is taken up, the catalysts are filtered off over Hyflo and the filtrate is evaporated, yielding 39 parts (100%) of N-(2-aminophenyl)-N′-(1-methylethyl)-N′-[1-(2-phenylethyl)-4-piperidinyl]thiourea as a residue.

Example XI

Following the procedure of Example X and using an equivalent amount of an appropriate nitro-compound as a starting material, there are prepared:

ethyl 4-[[[(2-aminophenyl)amino]thioxomethyl}methylamino]-1-piperidinecarboxylate;
ethyl 4-{[(2-aminophenyl)aminothioxomethyl]butylamino}-1-piperidinecarboxylate;
N-(2-aminophenyl-N′-[1-(2-phenylethyl)-4-piperidinyl]thiourea;
N-(2-aminophenyl)-N′-[1-(2-phenylethyl)-4-piperidinyl]-N′-propylthiourea;
N-(2-aminophenyl)-N′-cyclopropyl-N′-[1-(2-phenylethyl)-4-piperidinyl]thiourea;
methyl 4-{[(2-aminophenyl)amino]thioxomethylamino}-3-methyl-1-piperidinecarboxylate;
N-(2-aminophenyl)-N′-[1-(2-phenylethyl)-4-piperidinyl]-N′-(phenylmethyl)thiourea as a residue.

Example XII

A mixture of 23 parts of (phenylmethyl) 4-[{2-[(4-fluorophenylmethyl)amino]-3-pyridinylamino}-thioxomethylamino]-1-piperidinecarboxylate, 17 parts of mercury oxide, 0.1 parts of sulfur and 450 parts of tetrahydrofuran is stirred and refluxed for 1 hour. The reaction mixture is filtered over Hyflo and the filtrate is evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2′-oxybispropane. The product is filtered off and dried, yielding 20 parts (93%) of (phenylmethyl) 4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinecarboxylate; mp. 130°C.

Example XIII

Following the procedure of Example XII and using equivalent amounts of the appropriate starting materials there are prepared:

ethyl 4-[(1H-benzimidazol-2-yl)methylamino]-1-piperidinecarboxylate;
ethyl 4-[(1H-benzimidazol-2-yl)butylamino]-1-piperidinecarboxylate; mp. 225.9°C;
ethyl 4-[1-(phenylmethyl)-5-(trifluoromethyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 200°C;
ethyl 4-(5-fluoro-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 227.5°C;
ethyl 4-[5-chloro-1-(phenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 211.9°C;
ethyl 4-[3-(phenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinecarboxylate; mp. 148.6°C;
ethyl 4-[5-chloro-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 215.8°C.
methyl 4-(1H-benzimidazol-2-ylamino)-3-methyl-1-piperidinecarboxylate; mp. 155°C;
ethyl 4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridin-2-ylamino]-1-piperidinecarboxylate; mp. 134.4°C;
ethyl 4-[(3H-imidazo[4,5-b]pyridin-2-yl)amino]-1-piperidinecarboxylate; mp. 216.1°C;
ethyl 4-(1-phenyl-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 137°C; and
ethyl 4-[1-(4-fluorophenyl)-1H-benzimidazol-2-ylamino]-1-piperidinecarboxylate; mp. 153°C.

Example XIV

A mixture of 28 parts of ethyl 4-{[(2-aminophenyl)aminothioxomethyl]amino}-1-piperidinecarboxylate, 112 parts of iodo-methane and 240 parts of ethanol is stirred and refluxed for 8 hours. The reaction mxiture is evaporated and the residue is taken up in water. The whole is alkalized with ammonium hydroxide and the product is extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanol and 2,2'-oxybispropane. The product is filtered off and dried, yielding 7 parts (28%) of ethyl 4-(1H-benzimidazol-2-yl-amino)-1-piperidinecarboxylate.

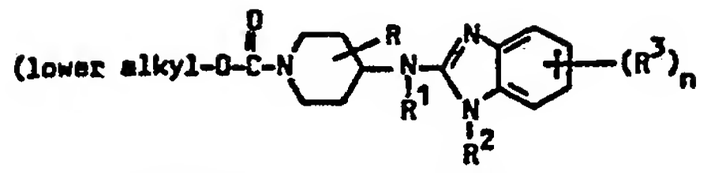
Following the same procedure and using equivalent amounts of the appropriate starting material there are prepared:
ethyl 4-(5-chloro-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate; mp. 234.1°C; and
ethyl 4-(5-methyl-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate.

Example XV

A mixture of 19 parts of methyl 4-(1H-benzimidazol-2-ylamino)-3-methyl-1-piperidinecarboxylate, 11 parts of 1-(chloromethyl)-4-fluorobenzene, 6 parts of sodium carbonate and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is cooled and poured onto water. The product is extracted three times with methylbenzene. The combined extracts are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure fractions are collected and the eluents is.evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 8 parts (38%) of methyl 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-3-methyl-1-piperidinecarboxylate; mp. 172.5°C.

Example XVI

Following the procedure of Example (XIII) the following 4-(1-R^2-1H-benzimidazol-2-ylamino)-1-piperidinecarboxylates are prepared by alkylating the corresponding 4-(1H-benzimidazol-2-ylamino)-1-piperidinecarboxylate with an appropriate chloride, bromide or iodide of the formula R^2X:



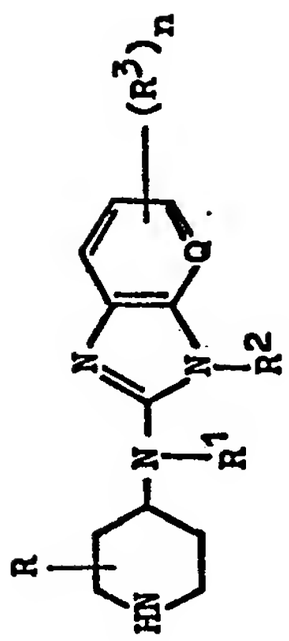
lower alkyl	R	R^1	R^2	$(R^3)_n$	melting point
C_2H_5	H	H	CH_3	H	166.7°C
C_2H_5	H	H	CH_3	5(6)–CH_3	142.0°C
C_2H_5	H	H	C_2H_5	H	–
C_2H_5	H	H	n.C_3H_7	H	–
C_2H_5	H	H	i.C_3H_7	H	–
C_2H_5	H	H	n.C_4H_9	H	–
C_2H_5	H	H	n.C_5H_{11}	H	–
C_2H_5	H	H	n-C_6H_{13}	H	–
C_2H_5	H	H	n.C_7H_{15}	H	–
C_2H_5	H	H		H	–
C_2H_5	H	H	4–Br–C_6H_4–CH_2	H	–
C_2H_5	H	H	C_6H_5–CH_2	5(6)–CH_3	179.3°C
C_2H_5	H	H	C_6H_5–CH_2	H	–
C_2H_5	H	H	2–Cl–C_6H_4–CH_2	H	213.4°C
C_2H_5	H	H	4–Cl–C_6H_4–CH_2	H	202.6°C
C_2H_5	H	H	4–CH_3–C_6H_4–CH_2	H	177.7°C
C_2H_5	H	H	4–F–C_6H_4–CH_2	H	–
C_2H_5	H	H	2–F–C_6H_4–CH_2	H	176.0°C
C_2H_5	H	H	4–F–C_6H_4–CH_2	5(6)–CH_3	173.3°C
C_2H_5	H	H	4–F–C_6H_4–CH_2	5(6)–F	182.5°C
C_2H_5	H	H	C_6H_5–CH_2	5(6)–F	184.0°C
C_2H_5	CH_3	H	C_6H_5–CH_2	H	191.0°C (cis+trans-isomer)
C_2H_5	H	H	4–NO_2–C_6H_4–CH_2	H	–
C_2H_5	H	CH_3	C_6H_5–CH_2	H	258.0°C (HCl-salt)
C_2H_5	H	H	4–F–2–CH_3–C_6H_3–CH_2	H	–

Example XVII

A mixture of 7 parts of ethyl 4-{[5(6)-fluoro-1-(4-fluorophenylmethyl)-1H-benzimidazol-2-yl]amino}-1-piperidinecarboxylate and 300 parts of hydrobromic acid solution 48% in glacial acetic acid is stirred and refluxed for 1 hour. The reaction mixture is evaporated and the residue is boiled in 2-propanol. 2,2'-Oxybispropane is added and upon cooling, the product is allowed to crystallize. It is filtered off and dried, yielding 7.2 parts (88.2%) of 5(6)-fluoro-1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydro bromide; mp. 285.6°C.

Example XVIII

Following the procedure of Example XVII the following 1-R^2-N-(4-piperidinyl)-1H-benzimidazol-2-amines are prepared by hydrolysing the corresponding methyl or ethyl 1-piperidinecarboxylates.



R	R^1	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
H	H	H	5-Cl	CH	2HBr	–
H	H	H	H	CH	2HBr	–
H	H	CH_3	5(6)-CH_3	CH	2HBr	–
H	H	H	5-CH_3	CH	2HBr	–
H	H	CH_3	H	CH	2HBr	–
H	H	C_2H_5	H	CH	2HBr.1/2H_2O	334–338°C
H	H	nC_3H_7	H	CH	2HBr	–
H	H	C_6H_5-CH_2	H	CH	2HBr	–
H	H	nC_5H_{11}	H	CH	base	–
H	H	nC_7H_{15}	H	CH	base	–
H	H	nC_4H_9	H	CH	base	–
H	H	nC_6H_{13}	H	CH	base	–
H	H		H	CH	base	–

R	R^1	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
H	H	iC_3H_7	H	CH	base	–
H	CH_3	H	H	CH	$2HBr.H_2O$	–
H	H	$2-Cl-C_6H_4-CH_2$	H	CH	base	–
H	H	$4-Cl-C_6H_4-CH_2$	H	CH	$2HBr.H_2O$	–
H	H	$4-Br-C_6H_4-CH_2$	H	CH	$2HBr.H_2O$	>300°C
H	H	$4-CH_3-C_6H_4-CH_2$	H	CH	2HBr	–
H	H	$4-F-C_6H_4-CH_2$	H	CH	2HBr	–
H	nC_4H_9	H	H	CH	$2HBr.H_2O$	223.1°C
H	H	$2-F-C_6H_4-CH_2$	H	CH	2HBr	–
H	H	$C_6H_5-CH_2$	$5-CF_3$	CH	2HBr	–
H	H	$C_6H_5-CH_2$	5–Cl	CH	2HBr	>260°C
H	H	$C_6H_5-CH_2$	H	N	$2HCl.H_2O$	298.1°C
H	H	$4-F-C_6H_4-CH_2$	5–Cl	CH	2HBr	>260°C
H	H	$4-F-C_6H_4-CH_2$	$5(6)-CH_3$	CH	2HBr	–
H	H	$C_6H_5-CH_2$	$5(6)-CH_3$	CH	2HBr	–
H	H	$C_6H_5-CH_2$	5(6)–F	CH	2HBr	>260°C
$3-CH_3$	H	$4-F-C_6H_4-CH_2$	H	CH	2HBr	–
$3-CH_3$	H	$C_6H_5-CH_2$	H	CH	$2HBr.H_2O$	250.2°C (cis+trans-isomer)
H	H	C_6H_5	H	CH	$2HBr.H_2O$	>300°C
H	H	$4-F-C_6H_4$	H	CH	2HBr	>300°C
H	H	$4-NO_2-C_6H_4-CH_2$	H	CH	2HBr	–
H	H	$4-F-2-CH_3-C_6H_3-CH_2$	H	CH	2HBr	–

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Example XIX

A mixture of 20 parts of (phenylmethyl) 4-[3-(4-fluorophenylmethyl)-3H-imidazo[4,5-b]pyridine-2-ylamino]-1-piperidinecarboxylate and 160 parts of methanol is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is boiled in 2,2'-oxybispropane. The undissolved product is filtered off and converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 12 parts of 3-(4-fluorophenylmethyl)-N-(4-piperidinyl)-3H-imidazo[4,5-b]pyridin-2-amine dihydrochloride monohydrate; mp. 269.7°C.

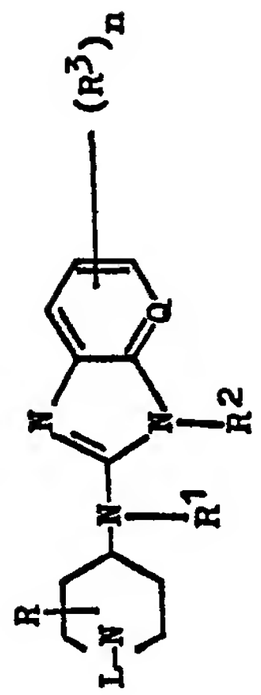
B. Preparation of final products:

Example XX

A mixture of 2 parts of 2-(bromoethoxy)benzene, 3 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine, 2 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70°C. The reaction mixture is cooled and poured onto water. The product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 3.5 parts (70%) of N-[1-(2-phenoxyethyl)-4-piperidinyl]-1-(phenylmethyl)-1H-benzimidazol-2-amine dihydrochloride monohydrate; mp. 197.6°C.

Example XXI

Following the procedure of Example XX and using equivalent amounts of the appropriate starting materials the following compounds are prepared in free base form or in the form of an acid addition salt after reacting the free base with an appropriate acid.



L	R	R¹	R²	$(R^3)_n$	Q	Base or Salt form	melting point
$C_6H_5-(CH_2)_2$	H	H	CH_3	H	CH	$2HCl.1/2\ H_2O$	298.3°C
						base	192.8°C
$C_6H_5-(CH_2)_2$	H	H	C_2H_5	H	CH	$2HCl.1/2\ H_2O$	278.8°C
						base	141.9°C
$C_6H_5-(CH_2)_2$	H	H	nC_3H_7	H	CH	$2HCl.H_2O$	243.5°C
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	H	CH	$2HCl.H_2O$	212.8°C
$C_6H_5-(CH_2)_2$	H	H	nC_5H_{11}	H	CH	$2HCl.1/2\ H_2O$	274.4°C
$C_6H_5-(CH_2)_2$	H	H	nC_7H_{15}	H	CH	$2HCl.H_2O$	224.2°C
$C_6H_5-(CH_2)_2$	H	H	nC_4H_9	H	CH	$2HCl.1/2\ H_2O$	285.6°C
$C_6H_5-(CH_2)_2$	H	H	nC_6H_{13}	H	CH	2HCl	295.8°C
$C_6H_5-(CH_2)_2$	H	H		H	CH	2HCl	299.6°C
$C_6H_5-(CH_2)_2$	H	H	iC_3H_7	H	CH	$2HCl.1/2\ H_2O$	244.4°C
$C_6H_5-(CH_2)_2$	H	H	H	H	CH	$2HCl.H_2O$	251.5°C
$C_6H_5-(CH_2)_2$	H	CH_3	2-Cl-$C_6H_4-CH_2$	H	CH		
$C_6H_5-(CH_2)_2$	H	H	4-Br-$C_6H_4-CH_2$	H	CH		

L	R	R^1	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
$C_6H_5-(CH_2)_2$	H	H	$4-CH_3-C_6H_4-CH_2$	H	CH	$2HCl.H_2O$	191.4°C
$C_6H_5-(CH_2)_2$	H	H	$4-F-C_6H_4-CH_2$	H	CH	2HCl	281.1°C
$C_6H_5-(CH_2)_2$	H	nC_4H_9	H	H	CH	base	183.4°C
$C_6H_5-(CH_2)_2$	H	H	$2-F-C_6H_4-CH_2$	H	CH	base	138.6°C
$C_6H_5-(CH_2)_2$	H	H	H	H	CH	base	192.1°C
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	$5-CF_3$	CH	2HCl	264.7°C
$C_6H_5-(CH_2)_2$	H	H	$4-F-C_6H_4-CH_2$	5-Cl	CH	base	168.3°C
$C_6H_5-(CH_2)_2$	H	H	$4-F-C_6H_4-CH_2$	$5(6)-CH_3$	CH	base	203–215°C
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	$5(6)-CH_3$	CH	base	181.9°C
$C_6H_5-(CH_2)_2$	H	H	$C_6H_5-CH_2$	5(6)-F	CH	base.1/2 H_2O	146.1°C
$C_6H_5-(CH_2)_2$	H	H	$4-F-C_6H_4-CH_2$	H	N	base	193.2°C
$C_6H_5-(CH_2)_2$	CH_3	H	$C_6H_5-CH_2$	H	CH	$2HCl.H_2O$	297.9°C (cis+trans-isomer)
$C_6H_5-(CH_2)_2$	CH_3	H	$4-F-C_6H_4-CH_2$	H	CH	$2HCl.H_2O$	220.3°C (cis+trans-isomer)
$4-NO_2-C_6H_4-(CH_2)_2$	H	H	$4-F-C_6H_4-CH_2$	H	CH	base	162.7°C
$C_6H_5-(CH_2)_3$	H	H	$C_6H_5-CH_2$	H	CH	$2HCl.H_2O$	197.1°C
$CH_2=CH-CH_2$	H	H	C_2H_5	H	CH	$2HNO_3.1/2\ H_2O$	258.1°C
$CH_2=CH-CH_2$	H	H	$C_6H_5-CH_2$	H	CH	$2HCl.H_2O$	261.9°C
$C_6H_5-O-(CH_2)_3$	H	H	$C_6H_5-CH_2$	H	CH	2HCl.1/2 H_2O	208.8°C

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L	R	R^1	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
$C_6H_5-O-(CH_2)_3$	H	H	$4-F-C_6H_4-CH_2$	H	CH	base	144.5°C
$C_6H_5-O-(CH_2)_3$	H	H	$4-F-C_6H_4-CH_2$	H	N	base	157.6°C
$C_6H_5-O-(CH_2)_3$	CH_3	H	$4-F-C_6H_4-CH_2$	H	CH	$2(COOH)_2H_2O$	141.3°C
$(C_6H_5)_2CH-(CH_2)_2$	H	H	$C_6H_5-CH_2$	H	CH	base	173.8°C
nC_4H_9	H	H	$C_6H_5-CH_2$	H	CH	$2HCl.H_2O$	273.3°C
$C_6H_5-CO-CH_2$	H	H	$C_6H_5-CH_2$	H	CH	$2HNO_3.3H_2O$	135.6°C
$(C_6H_5)_2CH$	H	H	$C_6H_5-CH_2$	H	CH	base	203.7°C
$C_6H_5-CH(CH_3)$	H	H	$C_6H_5-CH_2$	H	CH	base	154.0°C
$C_6H_5-CH(CH_3)-CH_2$	H	H	$C_6H_5-CH_2$	H	CH	$2HNO_3.H_2O$	159.0°C
$C_6H_5-CH(CH_3)$	H	H	$4-F-C_6H_4-CH_2$	H	CH	base	170–172.8°C
$C_6H_5-CH(CH_3)-CH_2$	H	H	$4-F-C_6H_4-CH_2$	H	CH	$2HNO_3-2H_2O$	155.4°C

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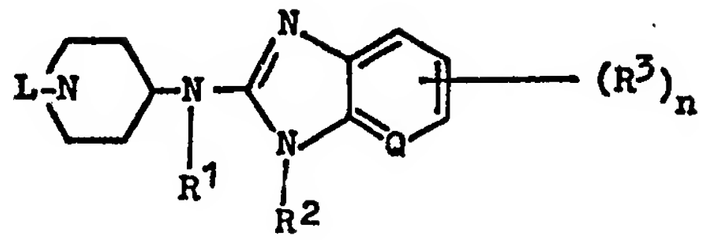
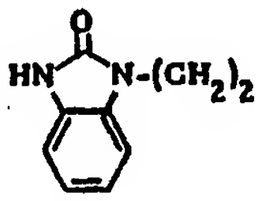
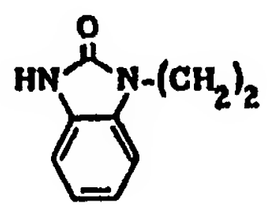
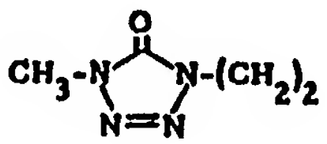
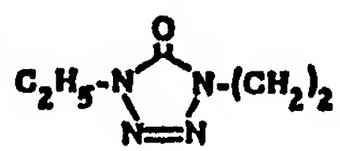
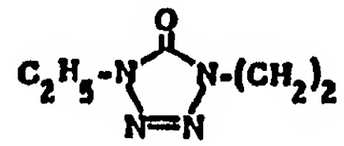
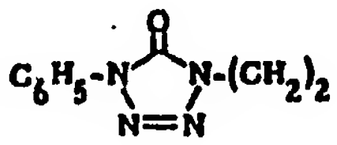
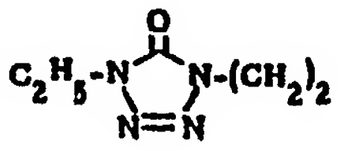
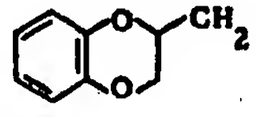
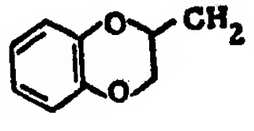


L	R^2	$(R^3)_n$	Q	Base or salt form	melting point
$4-CH_3O-C_6H_4-O-(CH_2)_3$	$4-F-C_6H_4-CH_2$	H	CH	base	143.1°C
$C_6H_5-CH=CH-CH_2$	$4-F-C_6H_4-CH_2$	H	CH	base.H_2O	155.5°C
$C_6H_5-CH=CH-CH_2$	$C_6H_5-CH_2$	H	CH	2HCl.H_2O	192.4°C
$C_6H_5-CH=CH-CH_2$	C_2H_5	H	CH	$2HNO_3.2H_2O$	136.0°C
$C_6H_5-CH=CH-CH_2$	$4-F-C_6H_4-CH_2$	H	N	base	152.8°C
$C_6H_5-O-(CH_2)_4$	$4-F-C_6H_4-CH_2$	H	CH	base	150.7°C
$4-F-C_6H_4-CO-(CH_2)_3$	$C_6H_5-CH_2$	H	CH	2HCl.1/2 H_2O	269.1°C
$4-F-C_6H_4-CO-(CH_2)_3$	C_2H_5	H	CH	2HCl	293.1°C
$C_6H_5-CH_2$	CH_3	H	CH	2HCl.$2H_2O$	241.0°C
$C_6H_5-CH_2$	$C_6H_5-CH_2$	H	CH	$2HNO_3.2H_2O$	147.2°C
$4-F-C_6H_4-CH_2$	$C_6H_5-CH_2$	H	CH	base	152.1°C
$C_6H_5(CH_2)_2$	$4-Cl-C_6H_4-CH_2$	H	CH	2HCl.1/2 H_2O	277.1°C
$4-F-C_6H_4-(CH_2)_2$	$4-F-C_6H_4-CH_2$	H	CH	2HCl.1/2 H_2O	283.7°C
$4-F-C_6H_4-(CH_2)_2$	$C_6H_5-CH_2$	H	CH	base	112.5°C
$3-CF_3-C_6H_4-(CH_2)_2$	$C_6H_5-CH_2$	H	CH	base	140.3°C

L	R^2	$(R^3)_n$	Q	Base or salt form	melting point
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3\text{-}$	H	H	CH	$2HCl.1/2\ H_2O$	279.4°C
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3\text{-}$	H	5-Cl	CH	2HCl	194.8°C
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3\text{-}$	H	$5\text{-}CH_3$	CH	$2HCl.1/2\ CH_3CHOHCH_3$	171.8°C
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3\text{-}$	$C_6H_5\text{-}CH_2$	H	CH	$2HNO_3.H_2O$	230.9°C
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3\text{-}$	CH_3	H	CH	$2HCl.H_2O$	271.7°C
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3\text{-}$	CH_3	$5(6)\text{-}CH_3$	CH	$2HCl.H_2O$	245.8°C
$(4\text{-}F\text{-}C_6H_4)_2CH\text{-}(CH_2)_3$	C_2H_5	H	CH	$2HCl.2H_2O$	208.6°C
	$C_6H_5\text{-}CH_2$	H	CH	base	237.5°C
	C_2H_5	H	CH	base	227.0°C
	$4\text{-}F\text{-}C_6H_4\text{-}CH_2$	H	CH	$2HCl.H_2O$	192.9°C
	$C_6H_5\text{-}CH_2$	H	CH	$2HCl.H_2O$	170.9°C

L	R^2	$(R^3)_n$	Q	Base or salt form	melting point
	4–F–C_6H_4–CH_2	H	CH	base	146.5°C
	CH_3	H	CH	2HCl.1/2 H_2O	279.6°C
	4–F–C_6H_4–CH_2	H	N	base	143.4°C
(4–F–C_6H_4)$_2$–CH–$(CH_2)_3$	(4–F–C_6H_4)$_2$–CH–$(CH_2)_3$	H	CH	base	171.1°C
	C_2H_5	H	CH	2HNO_3.H_2O	266.5°C
	C_6H_5–CH_2	H	CH	base	210.2°C

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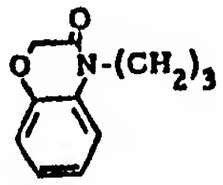
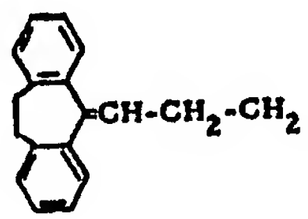
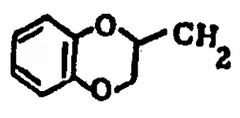
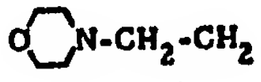
L	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
	$C_6H_5-CH_2$	H	CH	2. HOOC–CH=CH–COOH	196.2°C
$C_6H_5-CH_2-CH_2$	$C_6H_5-CH_2$	5–CL	CH	base	126.4°C
$C_6H_5-NH-(CH_2)_3$	4–F–$C_6H_4-CH_2$	H	CH	base	153.1°C
$C_6H_5-O-(CH_2)_3$	C_6H_5	H	CH	base	130.3°C
$C_6H_5-CH_2-CH_2$	C_6H_5	H	CH	base	131.0°C
$CH_3-(CH_2)_3$	C_6H_5	H	CH	base	125.3°C
$C_6H_5-CH=CH-CH_2$	C_6H_5	H	CH	base	147.1°C
$C_6H_5-CH_2-CH_2$	4–F–C_6H_4	H	CH	base	113.8°C
$C_6H_5-O-(CH_2)_3$	4–F–C_6H_4	H	CH	base	105.6°C
4–$CH_3O-C_6H_4-S-(CH_2)_3$	4–F–$C_6H_4-CH_2$	H	CH	base	114.5°C
$C_6H_5-CH_2-CH_2$	$C_6H_5-CH_2$	H	N	base	153.2°C
	4–F–$C_6H_4-CH_2$	H	CH	base	177.6°C

L	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
$4-(CH_3-S)-C_6H_4-(CH_2)_2$	$4-F-C_6H_4-CH_2$	H	CH	base	176.0°C
$4-(CH_3-SO_2)-C_6H_4-(CH_2)_2$	$4-F-C_6H_4-CH_2$	H	CH	1/2 $CH_3-CH(OH)-CH_3$	235.8°C
$(4-F-C_6H_4)_2-CH-(CH_2)_3$	$4-F-C_6H_4-CH_2$	H	CH	base	131.9°C
$CH_3-(CH_2)_3$	$C_6H_5-CH_2$	H	N	base	147.5°C
$C_6H_5-O-CH_2-CH_2$	$C_6H_5-CH_2$	H	N	base	142.5°C
$(C_6H_5)_2-CH-CH_2-CH_2$	$C_6H_5-CH_2$	H	N	base	141.4°C
$NC-CH_2$	$4-F-C_6H_4-CH_2$	H	CH	base	178.7°C
$4-F-C_6H_4-CO-(CH_2)_3$	$4-F-C_6H_4-CH_2$	H	N	base	161.5°C
$4-F-C_6H_4-O-(CH_2)_3$	$C_6H_5-CH_2$	H	N	base	124.9°C
	$C_6H_5-CH_2$	H	N	base	184.7°C
$CH_2=CH-CH_2$	$C_6H_5-CH_2$	H	N	base	132.6°C
$2,6-(CH_3)_2-C_6H_3-CO-CH_3$	$C_6H_5-CH_2$	H	N	base	176.8°C
	$C_6H_5-CH_2$	H	N	1/2 H_2O	153.3°C
$C_6H_5-CH=CH-CH_2$	$C_6H_5-CH_2$	H	N	base	124.6°C

L	R^2	$(R^3)_n$	Q	Base or Salt form	melting point
$4-F-C_6H_4-CO-(CH_2)_3$	$C_6H_5-CH_2$	H	N	base	141.0°C
$CH_3-(CH_2)_5$	$C_6H_5-CH_2$	H	N	base	137.3°C
$3-CN-3,3-(C_6H_4)_2-C-(CH_2)_2$	$4-F-C_6H_4-CH_2$	H	N	2 $HCl.H_2O$	188.9°C
$3-CN-3,3-(C_6H_4)_2-C-(CH_2)_2$	$C_6H_5-CH_2$	H	CH	2 $HNO_3.H_2O$	151.1°C
$3-CN-3,3-(C_6H_4)_2-C-(CH_2)_2$	CH_3-CH_2	H	CH	2 HNO_3. 1/2 H_2O	240.5°C

Example XXII

A mixture of 2.4 parts of (2-bromoethyl)benzene, 6 parts of 5(6)-fluoro-1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 4 parts of sodium carbonate, 0.2 parts of potassium iodide and 240 parts of 4-methyl-2-pentanone is stirred and refluxed overnight using a water-separator. The reaction mixture is cooled and poured onto water. The layers are separated and the aqueous phase is extracted three times with trichloromethane. The combined organic phases are dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is separated by column-chromatography over silica gel using a mixture of ethyl acetate and methanol (93:7 by volume) as eluent. The first fraction (A-isomer) is collected and the eluent is evaporated. The residue is washed with a mixture of 2,2′-oxybispropane and petroleumether, and dried, yielding 1 part (17.5%) of 6-fluoro-1-(4-fluorophenylmethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 178.1°C.

The second fraction (B-isomer) is collected and the eluent is evaporated. The residue is washed with a mixture of 2,2′-oxybispropane and petroleumether, and dried, yielding 1.2 parts of 5-fluoro-1-(4-fluorophenylmethyl)-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine monohydrate; mp. 188.8°C.

Example XXIII

A mixture of 4 parts of 1-(3-chloropropyl)-1,3-dihydro-3-(1-methylethenyl)-2H-benzimidazol-2-one, 7 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 5 parts of sodium carbonate, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanol. After stirring for 1 hour, the solvent is evaporated and the residue is taken up in water. The free base is liberated in the conventional manner with ammonium hydroxide and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from ethanol. The product is filtered off and dried, yielding 3.3 parts (45.7%) of 1,3 - dihydro - 1 - [3 - {4 - [1 - (phenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}-propyl] - 2H - benzimidazol - 2 - one; mp. 243.1°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

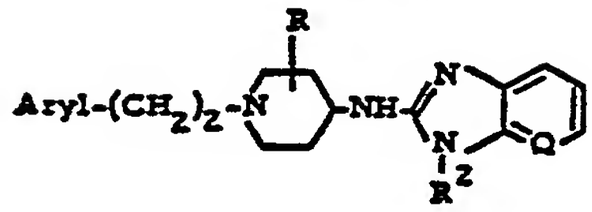
1 - [3 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}-propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 237.6°C;
1 - [3 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 3 - methyl - 1 - piperidinyl} - propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one dihydrochloride. 2-propanolate (1:1); mp. 244.1°C;
1 - [3 - {4 - [3 - (4 - fluorophenylmethyl) - 3H - imidazo[4,5 - b]pyridin - 2 - ylamino] - 1 - piperidinyl}propyl- 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 202.4°C.
1,3 - dihydro - 1 - {3 - [4 - (1 - phenyl - 1H - benzimidazol - 2 - ylamino) - 1 - piperidinyl]-propyl} - 2H - benzimidazol - 2 - one; mp. 185.3°C;
1 - [3 - {4 - [1 - (4 - fluorophenyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}propyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; 188.9°C; and
1,3 - dihydro - 1 - [3 - {4 - [3 - (phenylmethyl) - 3H - imidazo[4,5 - b]pyridin - 2 - ylamino] - 1 - piperidinyl} - propyl] - 2H - benzimidazol - 2 - one; mp. 221.7°C.

Example XXIV

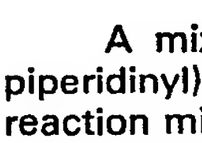
A mixture of 2.3 part of 2-(4-methoxyphenyl)ethyl methanesulfonate, 4.9 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 3.2 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70°C. The reaction mixture is poured onto water. The product is extracted with methylbenzene. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2′-oxybispropane, yielding 2.2 parts (48%) of 1 - (4 - fluorophenylmethyl) - N - {1 - [2 - (4 - methoxyphenyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine; mp. 172.9°C.

Example XXV

Following the procedure of Example XXIV and using equivalent amounts of the appropriate starting materials the following compounds are obtained in free base form or in the form of an acid addition salt after reacting the free base with an appropriate acid.



Aryl	R	R^2	Q	Base or salt form	melting point
3.4–$(CH_3O)_2$–C_6H_3	H	4–F–C_6H_4–CH_2	CH	base	69.3°C
2,5–$(CH_3O)_2$–C_6H_3	H	4–F–C_6H_4–CH_2	CH	base	127.9°C
4–(C_2H_5O)–C_6H_4	H	4–F–C_6H_4–CH_2	CH	base	152.3°C
4–(CH_3O)–C_6H_4	H	4–F–C_6H_4–CH_2	N	base	149.1°C
3–(CH_3O)–C_6H_4	H	4–F–C_6H_4–CH_2	CH	2HCl.1/2 H_2O	242.4°C
2–(CH_3O)–C_6H_4	H	4–F–C_6H_4–CH_2	CH	base	158.1°C
4–(CH_3O)–C_6H_4	CH_3	4–F–C_6H_4–CH_2	CH	2HCl	184.0°C (cis+trans-isomer)
3,4,5–$(CH_3O)_3$–C_6H_2	H	4–F–C_6H_4–CH_2	CH	2HCl.1/2 H_2O	260.2°C
3,4–$(CH_3O)_2$–C_6H_3	H	C_6H_5–CH_2	CH	base	149.8°C
4–(CH_3O)–C_6H_4	CH_3	C_6H_5–CH_2	CH	2HCl.H_2O	198.4°C (cis+trans-isomer)
3–(CH_3O)–C_6H_4	H	C_6H_5–CH_2	CH	base	128.6°C
4–(C_2H_5O)–C_6H_4	H	C_6H_5–CH_2	CH	base	128.5°C
2–(CH_3O)–C_6H_4	H	C_6H_5–CH_2	CH	2HCl.2H_2O	186.1°C
3–(CH_3)–C_6H_4	H	C_6H_5–CH_2	CH	2HCl.H_2O	235.7°C
4–(CH_3O)–C_6H_4	H	C_6H_5–CH_2	CH	2HCl.H_2O	274.7°C
4–Cl–C_6H_4	H	C_6H_5–CH_2	CH	base	183.9°C
3,4,5–$(CH_3O)_3$–C_6H_2	H	C_6H_5–CH_2	CH	base	156.6°C
4–$(C_6H_5CH_2O)$–C_6H_4	H	4–F–C_6H_4–CH_2	CH	base	155.4°C
4–CH_3O–C_3H_4	H	C_6H_5	CH	base	157.8°C
4–CH_3O–C_6H_4	H	4–F–C_6H_4	CH	base	167.4°C
4–CH_3O–C_6H_4	H	4–NO_2–C_6H_4–CH_2	CH	base	200.1°C

Aryl	R	R^2	Q	Base or Salt Form	Melting Point
$2,4-(CH_3O)_2-C_6H_3$	H	$4-F-C_6H_4-CH_2$	CH	2 HCl. 1/2 H_2O	190.4°C
$4-CH_3O-C_6H_4$	H	$4-F-2-CH_3-C_6H_3-CH_2$	CH	2 HBr	264.8°C
$4-CH_3O-C_6H_4$	H	$C_6H_5-CH_2$	N	base	124.1°C
$3-CH_3-4-(C_6H_5-CH_2-O)-C_6H_3$	H	$4-F-C_6H_4-CH_2$	CH	base	145.6°C
	H	$4-F-C_6H_4-CH_2$	CH	2 HCl.H_2O	264.6°C

Example XXVI

A mixture of 2.8 parts of [2-(2-thienyl)ethyl] 4-methylbenzenesulfonate, 4.9 parts of 1-[4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine dihydrobromide, 2.1 parts of sodium carbonate, 0.1 parts of potassium iodide and 90 parts of N,N-dimethylformamide is stirred overnight at 70°C. The reaction mixture is cooled and poured onto water. The product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanol. The product is filtered off and dried, yielding 2.3 parts (53% of 1-(4-fluorophenylmethyl)-N-{1-[2-(2-thienyl)ethyl]-4-piperidinyl}-1H-benzimidazol-2-amine; mp. 151.6°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

1 - (phenylmethyl) - N - {1 - [2 - (2 - thienyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine dihydrochloride. monohydrate; mp 259—273°C;
1 - (4 - fluorophenylmethyl) - N - {1 - [2 - (1 - naphthalenyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine; mp. 143.1°C; and
3 - (4 - fluorophenylmethyl) - N - {1 - [2 - (2 - thienyl)ethyl] - 4 - piperidinyl} - 3H - imidazo[4,5 - b]pyridin - 2 - amine; mp. 176.2°C.

Example XXVII

A mixture of 2.1 parts of 2-(ethenyl)pyridine, 3.25 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine and 80 parts of 1-butanol is stirred and refluxed overnight. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2′-oxybispropane, yielding 1 part (23%) of 1 - [(4 - fluorophenyl)methyl] - N - {1 - [2 - (2 - pyridinyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine; mp. 133.4°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinepropanenitrile; mp. 166.5°C;
1 - (4 - fluorophenylmethyl) - N - {1 - [2 - (4 - pyridinyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine; mp. 158.2°C; and
3 - (4 - fluorophenylmethyl) - N - {1 - [2 - (2 - pyridinyl)ethyl] - 4 - piperidinyl} - 3H - imidazo[4,5 - b]pyridin - 2 - amine; mp. 157.2°C.

Example XXVIII

To 3.96 parts of 1-(4-fluorobenzoyl)aziridine, dissolved in 16 parts of benzene, are added 3.25 parts of 1-[(4-fluorophenyl)methyl]-N-(4-piperidinyl)-1H-benzimidazol-2-amine, 90 parts of benzene and 45 parts of N,N-dimethylformamide. The whole is stirred and refluxed for 5 hours. The reaction mixture is cooled and poured onto water. The layers are separated and the aqueous phase is extracted with methylbenzene. The combined organic phases are dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2′-oxybispropane, yielding 1 part (19%) of 4 - fluoro - N - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] - benzamide; mp. 193.7°C.

Starting from 3 - (phenylmethyl) - N - (4 - piperidinyl) - 3H - imidazo[4,5 - b]pyridin - 2 - amine and following the same procedure there is also prepared:

4 - fluoro - N - [2 - {4 - [3 - (phenylmethy) - 3H - imidazo[4,5 - b]pyridin - 2 - ylamino] - 1 - piperidinyl}ethyl]benzamide; mp. 187.5°C.

Example XXIX

A mixture of 3.6 parts of [(4-methoxyphenoxy)methyl] oxirane, 4.9 parts of 1 - [(4 - fluorophenyl)methyl] - N - (4 - piperidinyl) - 1H - benzimidazol - 2 - amine dihydrobromide, 2.1 parts of sodium carbonate, 40 parts of methanol and 90 parts of benzene is stirred and refluxed overnight. The reaction mixture is filtered and the filtrate is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane. The product is filtered off and dried, yielding 2.6 parts (51%) of 4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - α - (4 - methoxyphenoxymethyl) - 1 - piperidineethanol; mp. 174.5°C.

Example XXX

Following the procedure of Example XXIX and using equivalent amounts of the appropriate starting materials there are also prepared:

α - (phenoxymethyl) - 4 - {[1 - (phenylmethyl) - 1H - benzimidazol - 2 - yl]amino} - 1 - piperidineethanol; mp. 146.6°C;

4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - α - (phenoxymethyl) - 1 - piperidineethanol; mp. 181.3°C;

4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 3 - methyl - α - (phenoxymethyl) - 1 - piperidineethanol dihydrochloride. monohydrate; mp. 163.3°C;

α - (4 - methoxyphenoxymethyl) - 4 - [1 - (phenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineethanol; mp. 162.7°C;

α - (2 - butoxyphenoxymethyl) - 4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineethanol; mp. 138.7°C;

α - (2,6 - dimethoxyphenoxymethyl) - 4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineethanol; mp. 140°C;

4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - α - (2 - methoxyphenoxymethyl) - 1 - piperidineethanol; mp. 174°C;

1 - {4 - [3 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl} - 2 - hydroxypropoxy]phenyl}ethanone; mp. 174.7°C;

α - (2,6 - dimethoxyphenoxymethyl) - 4 - [1 - (phenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineethanol; mp. 122.2°C;

4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - α - phenyl - 1 - piperidineethanol; mp. 184.1°C; and

α - (phenoxymethyl) - 4 - [3 - (phenylmethyl) - 3H - imidazo[4,5 - b]pyridin - 2 - ylamino] - 1 - piperidineethanol; mp. 136.6°C.

Example XXXI

To a stirred mixture of 40.4 parts of 1-(4-fluorophenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine hydrobromide and 400 parts of methanol are added 8.8 parts of oxirane and stirring is continued overnight at room temperature. The reaction mixture is evaporated and the residue is taken up in water. The precipitated product is filtered off and dried, yielding 29 parts (64%) of 4-[1-(4-fluorophenylmethyl)-1H-benzimidazol-2-ylamino]-1-piperidineethanol monohydrobromide; mp. 248.2°C.

Example XXXII

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol, are added 1.5 parts of formaldehyde solution 37%, 3 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The residue is taken up in water and the whole is alkalized with ammonium hydroxide. The product is extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 1.5 parts (36.6%) of N-(1-methyl-4-piperidinyl)-1-(phenylmethyl)-1H-benzimidazol-2-amine dihydrochloride monohydrate; mp. 191.1°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

1 - (4 - fluorophenylmethyl) - N - (1 - methyl - 4 - piperidinyl) - 1H - benzimidazol - 2 - amine; mp. 145.5°C;

N - (1 - cyclohexyl - 4 - piperidinyl) - 1 - 4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine; mp 168°C;
1 - (4 - fluorophenylmethyl) - N - [1 - (1 - methyl - 2 - phenylethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine; mp. 182.4°C;
1 - methyl - N - (1 - methyl - 4 - piperidinyl) - 1H - benzimidazol - 2 - amine dihydrochloride dihydrate; 300.6°C;
1 - ethyl - N - [1 - methylethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine; mp. 156.6°C;
N - (1 - methyl - 4 - piperidinyl) - 1 - phenyl - 1H - benzimidazol - 2 - amine; mp. 128.5°C;
3 - (4 - fluorophenylmethyl) - N - (1 - methyl - 4 - piperidinyl) - 3H - imidazo[4,5 - b]pyridin - 2 - amine; mp. 153.4°C; and
N - (1 - methyl - 4 - piperidinyl) - 3 - (phenylmethyl) - 3H - imidazo[4,5 - b]pyridin - 2 - amine; mp. 141.4°C.

Example XXXIII

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol, are added 2 parts of cyclohexanone, 3 parts of 1-(phenylmethyl)-N-(4-piperidinyl)-1H-benzimidazol-2-amine, 1 part of acetic acid and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The residue is taken up in water and the whole is alkalized with sodium hydroxide. The product is extracted with tetrahydrofuran. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2,2'-oxybispropane and 2-propanol, yielding 1.5 parts (38.5%) of N-(1-cyclohexyl-4-piperidinyl)-1-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 143°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

1 - phenyl - 4 - {4 - [1 - (phenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}-cyclohexanecarbonitrile; mp. 106—107°C;
4 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl} - 1 - phenylcyclohexanecarbonitrile dihydrochloride; mp. 275°C;
1 - [3 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}butyl] - 1,3 - dihydro - 2H - benzimidazol - 2 - one; mp. 234.8°C;
N - (1 - cyclohexyl - 4 - piperidinyl) - 3 - (phenylmethyl) - 3H - imidazo[4,5 - b]pyridin - 2 - amine; mp. 129.2°C;
N - [1 - (1 - methylethyl - 4 - piperidinyl] - 3 - (phenylmethyl) - 3H - imidazo[4,5 - b]pyridin - 2 - amine; mp. 136.4°C; and
1 - (4 - fluorophenylmethyl) - N - [1 - {2 - [(phenylmethyl)amino]ethyl} - 4 - piperidine] - 1H - benzimidazol - 2 - amine; mp. 135.6°C;

Example XXXIV

A mixture of 39.8 parts of N-(2-aminophenyl)-N'-ethyl-N'-[1-(2-phenylethyl)-4-piperidinyl]-thiourea, 15 parts of mercury oxide, 0.1 parts of sulfur and 400 parts of methanol is stirred and refluxed overnight. The reaction mixture is filtered hot over Hyflo and the filtrate is evaporated. The residue is crystallised from 4-methyl-2-pentanone. The product is filtered off and dried, yielding 14.5 parts (43%) of N-ethyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 204.9°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

N-[1-(2-phenylethyl)-4-piperidinyl]-N-propyl-1H-benzimidazol-2-amine;
N-(1-methylethyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 228.4°C;
N-cyclopropyl-N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine; mp. 193.5°C;
N-[1-(2-phenylethyl)-4-piperidinyl]-N-(phenylmethyl)-1H-benzimidazol-2-amine; mp. 191.5°C.

Example XXXV

To a stirred and cooled (below 5°C) mixture of 3.3 parts of N - methyl - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine, 100 parts of dimethylsulfoxide and 90 parts of benzene are added 0.5 parts of sodium hydride dispersion 50%. After stirring for 30 minutes, 1.5 parts of 1-(chloromethyl)-4-fluorobenzene are added and stirring is continued overnight while the mixture is allowed to reach room temperature. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from 2-propanol, yielding 2.8 parts (54.4%) of 1 - [(4 - fluorophenyl)methyl] - N - methyl - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine dihydrochloride; mp. 246.6°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

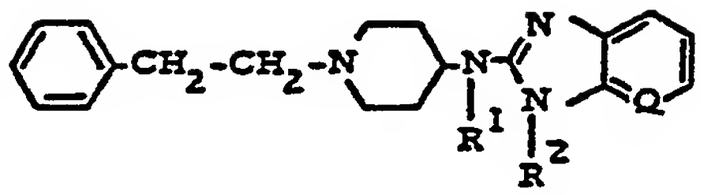
1 - [(4 - chlorophenyl)methyl] - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 138°C;
1 - [(2 - methoxyphenyl)methyl] - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 148.3°C;
1 - [(4 - methoxyphenyl)methyl] - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 122.4°C;
1 - [(4 - fluorophenyl)methyl] - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 108.5°C;
1 - (4 - bromophenylmethyl) - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 139.3°C;
1 - [(4 - methylphenyl)methyl] - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 123.4°C;
1 - (2 - chlorophenylmethyl) - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 105.5°C;
1 - butyl - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 76.5°C; and
1 - ethyl - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N - (phenylmethyl) - 1H - benzimidazol - 2 - amine dihydrochloride. dihydrate; mp. 157.2°C.

Example XXXVI

A mixture of 1.6 parts of 1-(1-chloroethyl)-4-fluorobenzene 3.2 parts of N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine, 1 part of sodium carbonate, 0.1 parts of potassium iodide and 120 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is cooled, poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2,2′-oxybispropane. The product is filtered off and dried, yielding 1.8 parts (40.7%) of 1 - [1 - (4 - fluorophenyl)ethyl] - N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine; mp. 161.7°C

Example XXXVII

Following the procedures of Examples XXXV and XXXVI and using equivalent amounts of the appropriate starting materials the following compounds are obtained in free base form or in the form of an acid addition salt after reacting the free base with an appropriate acid. In this Example, Q = CH.



R^1	R^2	Base or Salt form	melting point
H	$C_6H_5-(CH_2)_2$	base	136.1°C
H	$4-F-C_6H_4-(CH_2)_2$	base	151.5°C
H	$(4-F-C_6H_5)-CH(C_6H_5)$	$2HCl.H_2O$	239.6°C
H	$C_6H_5-CH(CH_3)-CH_2$	base	144.5°C
H		base	127.6°C
H	$C_6H_5-CH(CH_3)$	$2HCl.H_2O$	239.9°C
H	$(4-F-C_6H_4)_2CH$	base	172.5°C
H	$2-(CH_3O)-C_6H_4-CH_2$	base	128.5°C
CH_3	$2-(CH_3O)-C_6H_4-CH_2$	$2HNO_3$	169.7°C
CH_3	$2-Cl-C_6H_4-CH_2$	2HCl	251.2°C
CH_3	$4-Br-C_6H_4-CH_2$	$2HCl.H_2O$	187.1°C
CH_3	$4-(CH_3O)-C_6H_4-CH_2$	$2HNO_3$	163.5°C
CH_3	$C_6H_5-CH_2$	2HCl	243.1°C
CH_3	$4-(CH_3)-C_6H_4-CH_2$	$2HNO_3$	175.3°C
CH_3	$4-Cl-C_6H_4-CH_2$	2HCl	251.3°C
CH_3	$n.C_4H_9$	2HCl	257.9°C
CH_3	C_2H_5	$2HCl.H_2O$	243.1°C
C_2H_5	$C_6H_5-CH_2$	base	115.8°C
C_2H_5	C_2H_5	base	93.2°C
nC_3H_7	$C_6H_5-CH_2$	$2HCl.H_2O$	159.4°C
nC_3H_7	nC_4H_9	$(COOH)_2$	177.5°C
nC_3H_7	C_2H_5	2HCl	160.7°C
iC_3H_7	C_2H_5	$2HCl.1/2\ H_2O$	206.8°C
iC_3H_7	$C_6H_5-CH_2$	$(COOH)_2$	215.6°C
iC_3H_7	nC_4H_9	$(COOH)_2$	198.0°C
nC_4H_9	$C_6H_5-CH_2$	$2HCl.2H_2O$	160.0°C

R^1	R^2	Base or Salt form	melting point
nC_4H_9	4–Br–C_6H_4–CH_2	2HCl.2H_2O	137.2°C
nC_4H_9	nC_4H_9	2HCl.2H_2O	138.7°C
nC_4H_9	4–F–C_6H_4–CH_2	2HCl.2H_2O	135.5°C
	C_2H_5	2HCl.2H_2O	123.8°C

Example XXXVIII

A mixture of 3.2 parts of N-[1-(2-phenylethyl)-4-piperidinyl]-1H-benzimidazol-2-amine, 2.9 parts of [2-(2-thienyl)ethyl] 4-methylbenzenesulfonate, 1 part of sodium carbonate and 135 parts of 4-methyl-2-pentanone is stirred and refluxed overnight with water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2,2′-oxybispropane and 2-propanone, yielding 1 part (23.2%) of N-[1-(2-phenylethyl)-4-piperidinyl]-1-[2-(2-thienyl)ethyl]-1H-benzimidazol-2-amine; mp. 118.3°C.

Example XXXIX

To a stirred and cooled (below 5°C) mixture of 4 parts of N-[1-(2-phenylethyl)-4-piperidinyl]-1-(phenylmethyl)-1H-benzimidazol-2-amine, 100 parts of dimethyl sulfoxide and 90 parts of benzene are added 0.5 parts of sodium hydride dispersion 50%. After stirring for 30 minutes at a temperature below 5°C, 1.3 parts of (chloromethyl)benzene are added and stirring is continued for 4 hours while the mixture is allowed to reach room temperature. The reaction mixture is poured onto water and the produce is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the nitrate salt in 2-propanone. The salt is filtered off and dried, yielding 1.5 parts (24%) of N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - N,1 - bis - (phenylmethyl) - 1H - benzimidazol - 2 - amine dinitrate; mp. 156.9°C.

Example XL

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol are added 3.3 parts of 1 - (4 - fluorophenylmethyl) - N - [1 - [2 - (4 - nitrophenyl)ethyl] - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of methylbenzene and methanol (95:5 by volume) saturated with ammonia, as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanol, yield 1.3 parts (42%) of N - [1 - [2 - (4 - aminophenyl)ethyl] - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 195.4°C.

Following the same hydrogenation procedure and starting from the corresponding nitro-compound there is also prepared:

1 - [(4 - aminophenyl)methyl] - N - [1 - [2 - (4 - methoxyphenyl)ethyl] - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine monohydrate; mp. 142.6°C.

Example XLI

A mixture of 7.5 parts of 1 - (4 - fluorophenylmethyl) - N - [1 - [2 - [4 - (phenylmethoxy)-phenyl]ethyl] - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine and 120 parts of methanol is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is suspended in 2,2′-oxybis-propane. The product is filtered off and dried, yielding 5.5 parts (88.5%) of 4 - [2 - [4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl]ethyl]phenol hemihydrate; mp. 111.6°C.

Following the same hydrogenation procedure and starting from 1 - (4 - fluorophenylmethyl) - N - [1 - [2 - [3 - methyl - 4 - (phenylmethoxy)phenyl]ethyl] - 4 - piperidinyl] - 1H -

benzimidazol - 2 - amine there is also prepared 4 - {2 - [4 - {[1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - yl]amino} - 1 - piperidinyl]ethyl} - 2 - methylphenol dihydrochloride monohydrate; mp. 277.8°C.

A mixture of 8 parts of 1 - (4 - fluorophenylmethyl) - N - {1 - [2 - (3 - methoxyphenyl)-ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine and 225 parts of a hydrobromic acid solution 48% in acetic acid is stirred and refluxed for 3 hours. The reaction mixture is evaporated and the residue is taken up in water. The free base is liberated in the conventional manner with ammonium hydroxide and extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is purified twice by column-chromatography over silica gel using first a mixture of trichloromethane and methanol (98:2 by volume) and then a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 0.8 parts (9%) of 3 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - yl - amino] - 1 - piperidinyl}ethyl]phenol dihydrochloride, monohydrate; mp. 209.8°C.

Example XLII

A mixture of 1.2 parts of 3 - bromo - 1 - propene, 4 parts of 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenol, 1.4 parts of potassium carbonate and 160 parts of 2-propanone is stirred and refluxed overnight. The reaction mixture is filtered and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 1 part (19.9%) of 1 - (4 - fluorophenylmethyl) - N - [1{2 - [4 - (2 - propenyloxy)phenyl]ethyl} - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine dihydrochloride; mp. 224.7°C.

Example XLIII

A mixture of 15 parts of thionyl chloride, 4 parts of 4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineethanol dihydrochloride and 375 parts of trichloromethane is stirred and refluxed overnight. The precipitated product is filtered off and dried, yielding 13 parts (83%) of N - [1 - (2 - chloroethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine dihydrochloride; mp. >260°C.

Example XLIV

A mixture of 0.9 parts of morpholine, 4.8 parts of N - [1 - (2 - chloroethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine dihydrochloride, 3 parts of sodium carbonate, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 0.6 parts (12.5%) of [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] 4 - morpholine-carboxylate; mp. 144.8°C.

Example XLV

A mixture of 3.6 parts of morpholine, 4.8 parts of N - [1 - (2 - chloroethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine dihydrochloride, 0.1 parts of potassium iodide and 135 parts of N,N-dimethylformamide is stirred and heated overnight at 70°C. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in methanol. The salt is filtered off and dried, yielding 1 part (18.3%) of 1 - (4 - fluorophenylmethyl) - N - {1 - [2 - (4 - morpholinyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine trihydrochloride; mp. +300°C.

Example XLVI

To a stirred mixture of 4.5 parts of 4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineethanol, 2 parts of N,N-diethylethanamine and 195 parts of dichloromethane is added dropwise a solution of 1.7 parts of 4-methoxybenzoyl chloride in dichloromethane. Upon completion, stirring is continued overnight at room temperature. Water is added and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 2.5 parts (43.5%) of [2 -

{4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] 4-methoxybenzoate; dihydrochloride hemihydrate; mp. 189.2°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are also prepared:

{4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenyl} benzeneacetate; mp. 135.1°C;
{4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenyl} 4-methoxybenzoate; mp. 157.1°C;
{4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenyl}methyl carbonate; mp. 134.5°C; and
{4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenyl} (phenylmethyl) carbonate; mp. 147.8°C.

Example XLVII

A mixture of 1.2 parts of chloroacetonitrile, 6.7 parts of 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol-2-ylamino] - 1 - piperidinyl}ethyl]phenol, 2.8 parts of potassium carbonate and 160 parts of 2-propanone is stirred and refluxed overnight. The reaction mixture is poured onto water and the product is extracted with methylbenzene. The extract is dried, filtered and evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and dried, yielding 7.4 parts (78.6%) of {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy} acetonitrile dihydrochloride. monohydrate; mp. 224.6°C.

Following the same procedure and using equivalent amounts of the appropriate starting materials there are prepared:

ethyl 2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}-ethyl]phenoxy}acetate; mp. 109.1°C;
methyl 2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy}acetate; mp. 109.8°C; and
1 - [2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy}acetyl]piperidine dihydrochloride; mp. 247°C.

Example XLVIII

A mixture of 0.5 parts of isocyanatomethane, 4.5 parts of 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenol and 135 parts of tetrahydrofuran is stirred overnight at room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1 part (20%) of {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}-ethyl]phenyl} methylcarbamate; mp. 172.2°C.

By the addition-reaction of 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenol to 1 - isocyanatobutane there is also prepared: {4 - [2 - {4 - [1 - (4-fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] -1 - piperidinyl}ethyl]phenyl} butyl carbamate; mp. 142.5°C.

Example IL

A mixture of 9 parts of 4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidineacetonitrile and 200 parts of methanol, saturated with ammonia, is hydrogenated at normal pressure and at room temperature with 3 parts of Raney-nickel catalyst. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and crystallized from a mixture of 2-propanone and methanol, yielding 11 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine trihydrochloride; mp. 292.9°C.

Following the same hydrogenation procedure and starting from 4 - [1 - (4 - fluorophenylmethyl)-1H - benzimidazol - 2 - ylamino] - 1 - piperidinepropanenitrile there is also prepared: N - [1 - (3 - amino-propyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine trihydrochloride. monohydrate; mp. 239.3°C.

Example L

A mixture of 1.8 parts of 1-isothiocyanato-2-nitrobenzene, 3.7 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine and 135 parts of tetrahydrofuran is stirred overnight at room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 3.7 parts (67%) of N - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] - N′ - (2 - nitrophenyl)thiourea as a residue.

A mixture of 3.7 parts of N - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] - N′ - (2 - nitrophenyl)thiourea, 7 parts of iron-powder, 0.25 parts of concentrated hydrochloric acid, 48 parts of ethanol and 15 parts of water is stirred and refluxed for 1 hour. The reaction mixture is alkalized with methanol saturated with ammonia. The whole is filtered and the filtrate is evaporated, yielding 3.5 parts of N - (2 - aminophenyl) - N′ - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl} - ethyl]thiourea as a residue.

A mixture of 3.5 parts of N - (2 - aminophenyl) - N′ - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]thiourea, 2.2 parts of mercury (II) oxide, 0.1 parts of sulfur and 80 parts of ethanol is stirred and refluxed for 1 hour. The reaction mixture is filtered over Hyflo and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanone, yielding 1.5 parts (44.4%) of N - {1 - [2 - (1H - benzimidazol - 2 - ylamino-ethyl] - 4 - piperidinyl} - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 253.4°C.

Example LI

A solution of 4.77 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine trihydrochloride in methanol saturated with ammonia is stirred for 1 hour at room temperature. The solvent is evaporated and the residue is taken up in 135 parts of tetrahydrofuran. Then there are added 6 parts of isocyanatomethane and the whole is stirred overnight at room temperature. The precipitated product is filtered off and dried, yielding 3 parts (70.7%) of N - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] - N′ - methylurea. hemihydrate; mp. 231.4°C.

Example LII

To a stirred mixture of 3.8 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine, 1 part of N,N-diethylethanamine and 195 parts of dichloromethane is added dropwise a solution of 1.7 parts of 4-methoxybenzoyl chlorine in dichloromethane. Upon completion, stirring is continued overnight at room temperature. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the hydrochloride salt in 2-propanol. The salt is filtered off and dried, yielding 1 part of N - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] - 4 - methoxy - N - (4 - methoxybenzoyl)benzamide dihydrochloride. dihydrate; mp. 161.5°C.

Example LIII

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol are added 1 part of paraformaldehyde, 3.5 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off and the filtrate is evaporated. The residue is taken up in water and the product is extracted with trichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2′-oxybispropane, yielding 1.5 parts (42%) of N - {1 - [2 - (dimethylamino)ethyl] - 4 - piperidinyl} - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 166.1°C.

Example LIV

To 1 part of a solution of 2 parts of thiophene in 40 parts of ethanol are added 2.5 parts of benzaldehyde, 3.7 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine and 120 parts of methanol. The whole is hydrogenated at normal pressure and at room temperature with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up, the catalyst is filtered off over Hyflo and the filtrate is evaporated. The residue is converted into the hydrochloride salt in 2-propanone. The salt is filtered off and taken up in water. The free base is liberated in the conventional manner with

ammonium hydroxide and extracted with dichloromethane. The extract is dried, filtered and evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2′-oxybispropane, yielding 1.5 parts (27.5%) of N - [1 - {2 - [bis(phenylmethyl)amino]ethyl} - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 116.4°C.

Example LV

A mixture of 5.5 parts of N - [1 - (1H - benzimidazol - 2 - yl) - 4 - piperidinyl] - 1 - (phenylmethyl) - 1H - benzimidazol - 2 - amine dinitrate, 1.5 parts of 1 - (chloromethyl) - 4 - fluorobenzene, 5 parts of sodium carbonate, 0.1 parts of potassium iodide and 120 parts of 4-methyl-2-pentanone is stirred and refluxed overnight using a water-separator. The reaction mixture is poured onto water and the layers are separated. The organic phase is dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 4-methyl-2-pentanone and 2,2′-oxybispropane. The product is filtered off and dried, yielding 1.5 parts (28.3%) of N - {1 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - yl] - 4 - piperidinyl} - 1 - (phenylmethyl) - 1H - benzimidazol - 2 - amine; mp. 163.9°C.

Example LVI

A mixture of 3.7 parts of 1 - (4 - fluorophenylmethyl) - N - {1 - [3 - (4 - methoxyphenylthio)-propyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine, 2.42 parts of hydrogen peroxide solution 30% and 20 parts of acetic acid is stirred and refluxed for 1 hour. The reaction mixture is cooled and poured onto ice-water. The whole is alkalized with sodium hydroxide solution 50% and the product is extracted with trichloromethane. The extract is washed with water, dried, filtered and evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is converted into the ethanedioate salt in methanol and 2-propanol. The salt is filtered off and dried, yielding 0.8 parts (16%) of 1 - (4 - fluorophenylmethyl) - N - {1 - [3 - (4 - methoxyphenyl-sulfonyl)propyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine ethanedioate (1:2); mp. 213.1°C.

Example LVII

A mixture of 5 parts of ethyl 2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimid-azol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy}acetate, 70 parts of ethanamine solution 50% and 40 parts of methanol is stirred for 3 hours at room temperature. The reaction mixture is evaporated and the residue is crystallized twice from 2-propanol, yielding 1 part (19%) of N - ethyl - 2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenoxy}acetamide; mp. 160.9°C.

Example LVIII

A mixture of 3.5 parts of methyl 2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy acetate, 90 parts of concentrated ammonium hydroxide and 40 parts of methanol is stirred for 4 hours at room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from 2-propanol, yielding 1 part (28.5%) of 2 - {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}-ethyl] - phenoxy}acetamide; mp. 180.4°C.

Example LIX

To a stirred and cooled (below 10°C) mixture of 5.04 parts of carbon disulfide, 2.06 parts of N,N′-methanetetraylbis[cyclohexamine] and 45 parts of tetrahydrofuran is added dropwise a solution of 3.7 parts of N - [1 - (2 - aminoethyl) - 4 - piperidinyl] - 1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - amine in tetrahydrofuran. Upon completion, stirring is continued overnight while the mixture is allowed to reach room temperature. The reaction mixture is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated, yielding 4 parts (100%) of 1 - (4 - fluorophenylmethyl) - N - [1 - (2 - isothiocyanatoethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine as a residue.

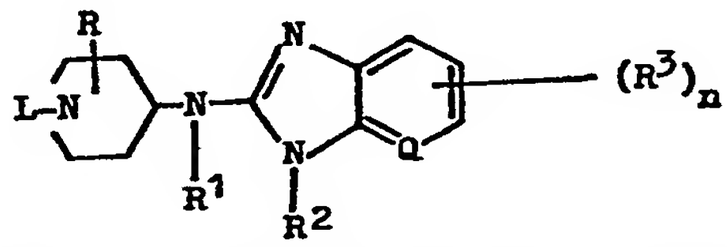
A mixture of 2.1 parts of N - (4 - fluorophenylmethyl) - 1,2 - benzenediamine, 4 parts of 1 - (4 - fluorophenylmethyl) - N - [1 - (2 - isothiocyanatoethyl) - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine and 90 parts of tetrahydrofuran is stirred and refluxed for 2 hours. the reaction mixture is evaporated, yielding 6 parts (100%) of N - {2 - [(4 - fluorophenylmethyl)amino]-phenyl} - N′ - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]thiourea as a residue.

A mixture of 6 parts of N - {2 - [(4 - fluorophenylmethyl)amino]phenyl} - N′ - [2 - {4 - [1 -

(4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]thiourea, 3.2 parts of mercury (II) oxide, 0.1 parts of sulfur, and 90 parts of tetrahydrofuran is stirred and refluxed for 3 hours. The reaction mixture is filtered over Hyflo and the filtrate is evaporated. The residue is purified by column-chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions are collected and the eluent is evaporated. The residue is crystallized from a mixture of 2-propanone and 2,2'-oxybispropane, yielding 1.2 parts (20%) of 1 - (4 - fluorophenylmethyl) - N - [1 - {2 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino]ethyl} - 4 - piperidinyl] - 1H - benzimidazol - 2 - amine; mp. 196.9°C.

Claims

1. A chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein

R is a member selected from the group consisting of hydrogen and C_1—C_6 alkyl;

R^1 is a member selected from the group consisting of hydrogen, C_1—C_6 alkyl, C_3—C_6 cycloalkyl, aryl-C_1—C_6-alkyl and C_1—C_6 alkanoyl;

R^2 is a member selected from the group consisting of hydrogen, alkyl having from 1 to 10 carbon atoms, aryl, C_3—C_6 cycloalkyl and mono- and diaryl(C_1—C_6 alkyl);

R^3 is a member independently selected from the group consisting of, halo, C_1—C_6 alkyl, C_1—C_6 alkyloxy and trifluoromethyl;

n is an integer of from 0 to 2 inclusive;

Q is a member selected from the group consisting of CH and N; and

L is a member selected from the group consisting of C_1—C_6 alkyl, which is optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, hydroxy, isothiocyanato, C_1—C_6 alkyloxy, aryl, aryloxy, arylthio, arylsulfonyl, amino; C_3—C_6 alkenyl; aryl-C_3—C_6-alkenyl; C_3—C_6 cycloalkyl, being optionally substituted with a cyano and/or an aryl group; 1-(aryl-C_1—C_6-alkyl)-1H-benzimidazol-2-yl; and a radical of the formula Z—C_mH_{2m}—, wherein

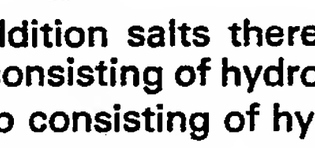
m is an integer of from 1 to 6 inclusive; and

Z is a member selected from the group consisting of 4,5-dihydro-5-oxo-1H-tetrazol-1-yl, being optionally substituted in its 4-position by an aryl radical or a C_1—C_6 alkyl radical; 2,3-dihydro-1,4-benzodioxin-2-yl; 2,3-dihydro-1,4-benzodioxin-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazin-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)methyl- 4-morpholinyl; 1-piperidinyl; 1-pyrrolidinyl; a radical of the formula T—N(R^4)—, wherein

R^4 is a member selected from the group consisting of hydrogen, C_1—C_6 alkyl and aryl-C_1—C_6-alkyl; and

T is a member selected from the group consisting of C_1—C_6 alkyl, aryl, aryl-C_1—C_6-alkyl, 1H-benzimidazol-2-yl; and

a radical of the formula



wherein

s is the integer 0 or 1;

X is a member selected from the group consisting of O and —N(R^5)—, said R^5 being a member selected from the group consisting of hydrogen, C_1—C_6 alkyl, aryl-C_1—C_6-alkyl, C_1—C_6 alkanoyl and aroyl; and

W is a member selected from the group consisting of C_1—C_6 alkyl, aryl, aryl-C_1—C_6-alkyl, amino, arylamino, mono- and di(C_1—C_6 alkyl)amino, mono- and di(aryl-C_1—C_6-alkyl)amino, 1-piperidinyl, 1-pyrrolidinyl and 4-morpholinyl;

wherein aryl as used in the foregoing definitions, is a member selected from the group consisting of phenyl, substituted phenyl, naphthalenyl, thienyl, halothienyl, (C_1—C_6 alkyl)thienyl, pyridinyl, mono- and di(C_1—C_6 alkyloxy)pyridinyl, furanyl and 1-(C_1—C_6 alkyl)pyrrolyl; wherein said substituted phenyl is phenyl having from 1 to 3 substituents each independently selected from the group consisting of halo, hydroxy, nitro, cyano, trifluoromethyl, C_1—C_6 alkyl, C_1—C_6 alkylthio, C_1—C_6 alkylsulfonyl, C_1—C_6 alkylsulfonyl-C_1—C_6 alkyl, phenyl-C_1—C_6-alkylsulfonyl, phenylsulfonyl-C_1—C_6 alkyl, amino, mono- and di-(C_1—C_6 alkyl)amino, C_1—C_6 alkanoyl, a radical of the formula R^6—C_pH_{2p}—O—, wherein

p is an integer of from 1 to 6 inclusive; and

R^6 is a member selected from the group consisting of hydrogen, amino, cyano, phenyl, aminocarbonyl, mono- and di(C_1—C_6 alkyl)aminocarbonyl, C_1—C_6 alkyloxycarbonyl, phenyl-C_1—C_6-alkyloxycarbonyl, 4-morpholinylcarbonyl, 1-piperidinylcarbonyl and 1-pyrrolidinylcarbonyl, C_3—C_6 alkenyl; and a radical of the formula R^7—O—, wherein

R^7 is a member selected from the group consisting of C_1—C_6 alkanoyl, phenylcarbonyl, phenyl-C_1—C_6-alkylcarbonyl, C_1—C_6 alkyloxycarbonyl, phenyl-C_1—C_6-alkyloxycarbonyl, aminocarbonyl, phenylaminocarbonyl, mono- and di-(C_1—C_6 alkyl)aminocarbonyl,

wherein said phenyl in the definition of said R^7 may be optionally substituted with up to 3 substituents each independently selected from the group consisting of halo, cyano, nitro, C_1—C_6 alkyl and C_1—C_6 alkyloxy; and wherein said aroyl in the definition of said X represents arylcarbonyl wherein said aryl is as defined hereabove.

2. A chemical compound selected from the group consisting of 1 - (4 - fluorophenylmethyl) - N-{1 - [2 - (4 - methoxyphenyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2 - amine and the pharmaceutically acceptable acid addition salts thereof.

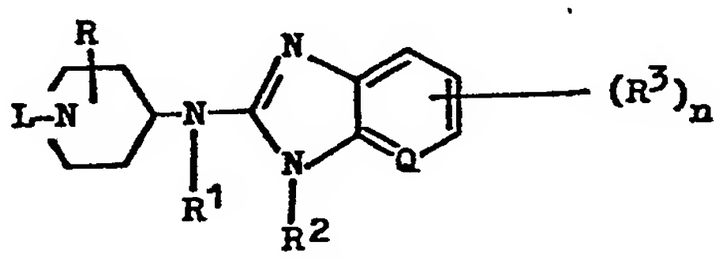
3. A chemical compound selected from the group consisting of 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenol and the pharmaceutically acceptable acid addition salts thereof.

4. A chemical compound selected from the group consisting of {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenyl} benzeneacetate and the pharmaceutically acceptable acid addition salts thereof.

5. A chemical compound selected from the group consisting of {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy} acetonitrile and the pharmaceutically acceptable acid addition salts thereof.

6. A chemical compound selected from the group consisting of N - [1 - (2 - phenylethyl) - 4-piperidinyl] - 1 - (phenylmethyl) - 1H - benzimidazol - 2 - amine and the pharmaceutically acceptable acid addition salts thereof.

7. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula

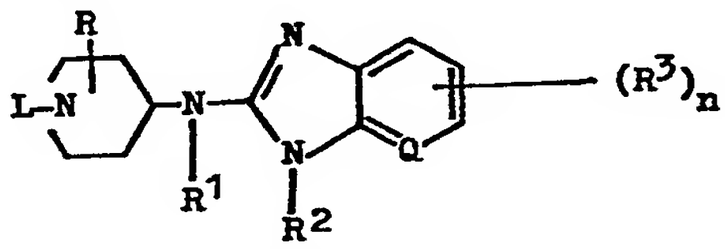


(I)

as defined in claim 1 and the pharmaceutically acceptable acid addition salts thereof.

8. An antihistaminic pharmaceutical composition comprising an inert carrier material and as an active ingredient an effective antihistaminic amount of a compound as claimed in any one of Claims 2 to 6.

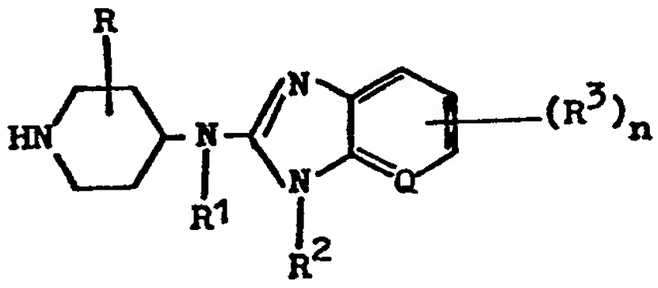
9. A process for preparing a chemical compound selected from the group consisting of a N-heterocyclyl-4-piperidinamine having the formula



(I)

and the pharmaceutically acceptable acid addition salts thereof, wherein L, R, R^1, R^2, R^3, Q, and n are as defined in Claim 1; characterized by

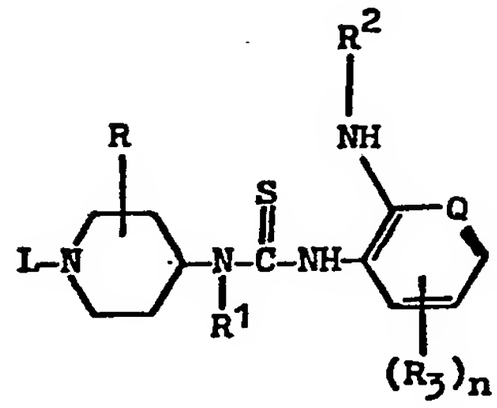
a) introducing onto a starting material of the formula



(II)

wherein R, R^1, R^2, R^3, n and Q are as previously defined, the desired L-substituent onto the piperidine nitrogen by the application of art-known methods; or

b) preparing compounds of formula (I) by the cyclodesulfurization of an appropriate thiourea derivative of the formula



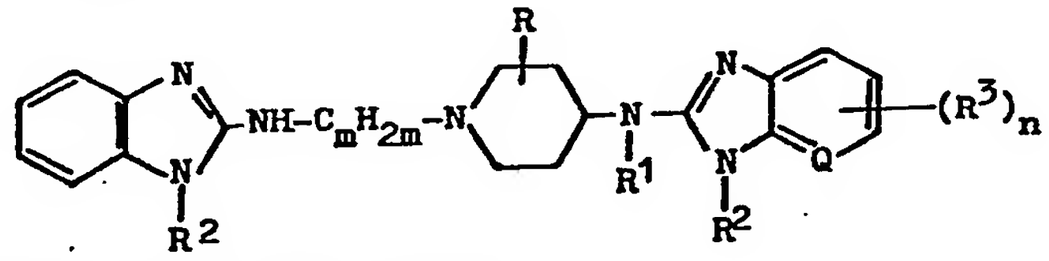
(V)

or

c) preparing compounds of formula (I) wherein R^2 is other than hydrogen, said R^2 being represented by R^2_a and said compounds by the formula (I-a), starting from a corresponding compound (I) wherein R^2 is hydrogen, (I-b), by introducing said R^2_a according to art-known procedures; or

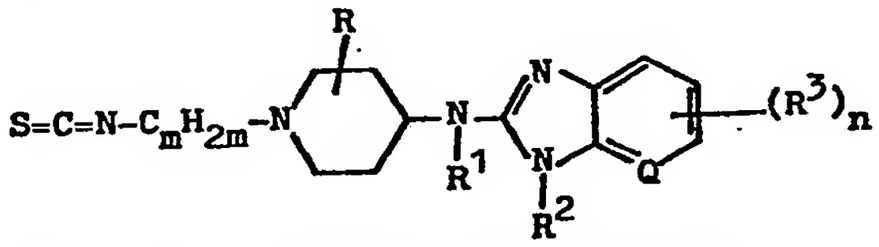
d) preparing compounds of the formula (I) wherein R^1 and R^2 are both different from hydrogen, said R^1 being represented by R^1_a and said R^2 by R^2_a, from the corresponding compounds wherein R^1 is hydrogen by introducing the R^1_a-group in a similar manner as described hereinabove in step c) for the preparation of compound (I-b) starting from (I-a); or

e) preparing a compound of the formula



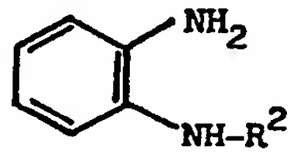
(I-c)

by subjecting an isothiocyanate of the formula



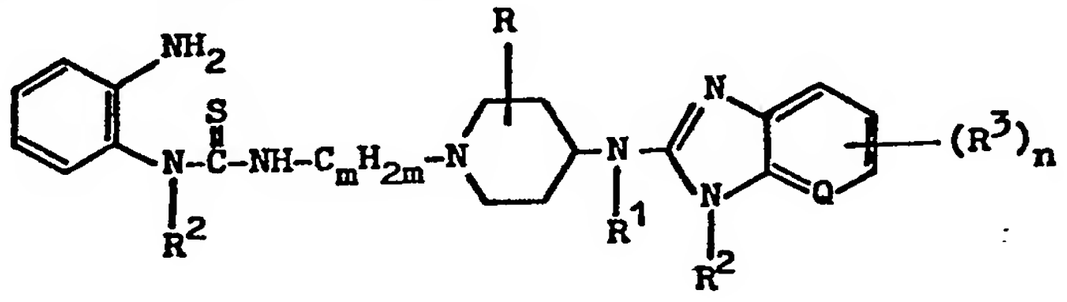
(VII)

to an addition reaction with a benzene diamine of the formula



(VIII)

and subsequently cyclodesulfurizing the intermediately formed thiourea of the formula



(IX)

or

f) preparing compounds of formula (I) wherein L represents a radical $Z—C_mH_{2m}—$, wherein Z represents a radical of the formula $W—CO—(X)_s—$, wherein s is 1, X is O and W is an optionally substituted amine, a 1-pyrrolidinyl, a 4-morpholinyl or a 1-piperidinyl radical, said compounds being represented by the formula (I-d), by the reaction of the corresponding amine, pyrrolidine, morpholine or piperidine with an appropriate N-[1-(halo-C_1—C_6-alkyl)-4-piperidinyl]-1H-benzimidazol-2-amine in the presence of an appropriate carbonate; or

g) preparing compounds of formula (I) which contain at least one hydroxyl-group as a substituent, from the corresponding phenylmethoxy substituted compounds by subjecting the latter to a catalytic hydrogenation in the presence of an appropriate catalyst, or deriving said hydroxyl-derivatives from the corresponding C_1—C_6 alkyloxy substituted analogs by hydrolyzing the latter in acidic medium, using for example hydrogen bromide in acetic acid, and, if desired, said hydroxyl-substituted compounds may in turn be O-alkylated or acylated by reacting the latter with a halide, a C_1—C_6 alkanoyl halide; an alkyloxycarbonyl halide, or an isocyanate, or said hydroxyl-substituted compounds may also be converted into halides by reacting therewith a suitable halogenating agent; or

h) deriving amino-substituted compounds from the corresponding nitro- and cyano-substituted compounds by reducing the latter, e.g., by catalytic hydrogenation in the presence of an appropriate catalyst, and, if desired, said amino-substituted compounds may in turn be N-alkylated or acylated by the reaction thereof with an appropriate alkylating agent or acylating agent; or

i) preparing secondary and tertiary amino-substituted compounds of formula (I) by substituting, for example, an appropriate halo-substituted ccmpound with the desired primary or secondary amine; or

j) deriving aminocarbonyl-substituted compounds from the corresponding esters by reacting the latter with ammonia or an appropriate primary- or a secondary amine in a suitable solvent; or

k) deriving compounds of formula (I) which contain in their structure a sulfonyl group from the corresponding thio compounds by oxidizing the latter with an appropriate oxidizing agent; and, if desired, converting the compounds of formula (I) to the therapeutically active non-toxic acid addition salt form by treatment with an appropriate acid, or the salt form can be converted by treatment with alkali into the free base form.

10. A process for preparing a chemical compound selected from the group consisting of 1 - (4-fluorophenylmethyl] - N - {1 - [2 - (4 - methoxyphenyl)ethyl] - 4 - piperidinyl} - 1H - benzimidazol - 2-amine and the pharmaceutically acceptable acid addition salts thereof, characterized by reacting 1 - [(4 - fluorophenyl)methyl] - N - (4 - piperidinyl) - 1H - benzimidazol - 2 - amine dihydrobromide with 2 - (4 - methoxyphenyl) ethylmethanesulfonate.

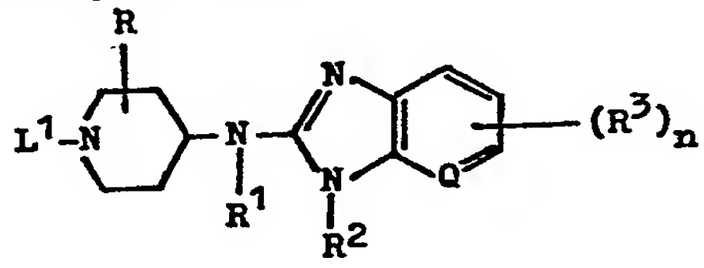
11. A process for preparing a chemical compound selected from the group consisting of 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenol and the pharmaceutically acceptable acid addition salts thereof, characterized by hydrogenating 1 - (4 - fluorophenylmethyl) - N - [1 - {2 - [4 - (phenylmethoxy)phenyl]ethyl} - 4 - piperidinyl] - 1H-benzimidazole - 2 - amine.

12. A process for preparing a chemical compound selected from the group consisting of {4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenyl} benzeneacetate and the pharmaceutically acceptable acid addition salts thereof, characterized by reacting 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl] - phenol with benzeneacetylchloride.

13. A process for preparing a chemical compound selected from the group consisting of {4 - [2-{4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]phenoxy}-acetonitrile and the pharmaceutically acceptable acid addition salts thereof, characterized by reacting 4 - [2 - {4 - [1 - (4 - fluorophenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl}ethyl]-phenol with chloroacetonitrile.

14. A process for preparing N - [1 - (2 - phenylethyl) - 4 - piperidinyl] - 1 - (phenylmethyl) - 1H-benzimidazol - 2 - amine, characterized by reacting 1 - (phenylmethyl) - N - (4 - piperidinyl) - 1H - benzimidazol - 2 - amine dihydrobromide with (2 - bromoethyl)benzene.

15. A chemical compound having the formula

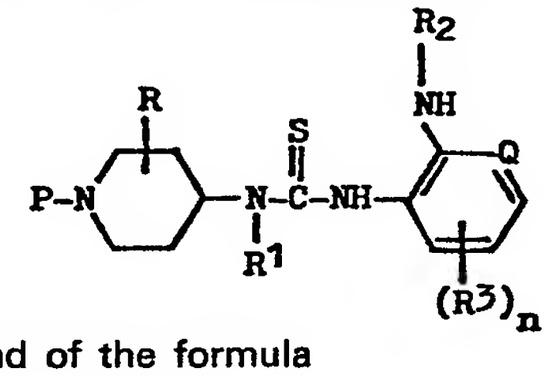


wherein:

L^1 is a member selected from the group consisting of hydrogen, C_1—C_6 alkyloxycarbonyl and phenylmethoxycarbonyl; and

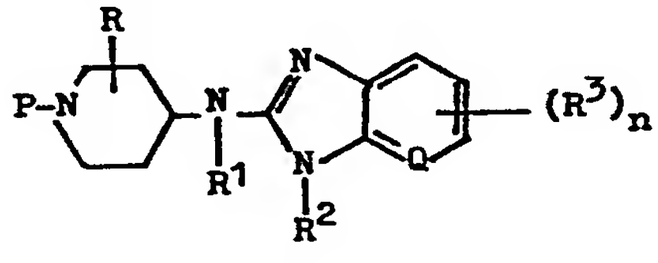
R, R^1, R^2, R^3, Q, and n are as defined in Claim 1.

16. A process for preparing a chemical compound according to Claim 15 characterized by cyclodesulfurizing, by known methods, a compound of formula



(X)

in order to prepare a compound of the formula



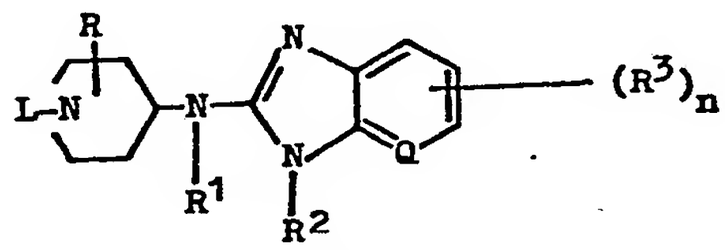
(XI)

wherein P is C_1—C_6 alkoxycarbonyl or phenylmethoxycarbonyl, and, if desired, eliminating said group P in order to prepare the compound in which L′ is hydrogen, when said group P is a C_1—C_6 alkyloxycarbonyl group it may be removed by alkaline or acid hydrolysis, using for example, hydrobromic acid in glacial acetic acid, and when said protecting group is a phenylmethoxycarbonyl group it may be removed by alkaline or acid hydrolysis or by catalytic hydrogenation using an appropriate catalyst such as palladium-on-charcoal.

17. A compound as claimed in any one of Claims 1 to 6 or a composition as claimed in Claim 7 or Claim 8 for use as an antihistaminic agent.

Patentansprüche

1. Chemische Verbindung aus der Gruppe der N-Heterocyclyl-4-piperidinamine der allagemeinen Formel



(I)

und ihre pharmazeutisch verträglichen Säure-additionssalze in der

R ein Wasserstoffatom oder einen C_1—C_6-Alkylrest bedeutet;

R^1 ein Wasserstoffatom, einen C_1—C_6-Alkyl-, C_3—C_6-Cycloalkyl-, Aryl-C_1—C_6-alkyl oder C_1—C_6-Alkanoylrest bedeutet;

R^2 ein Wasserstoffatom, einen Alkylrest mit 1 bis 10 Kohlenstoffatomen, einen Arylrest, C_3—C_6-Cycloalkylrest oder einen Mono- oder Diaryl-C_1—C_6-alkylrest darstellt;

R^3 einen unabhängig aus der Gruppe Halogenatom, C_1—C_6-Alkylrest, C_1—C_6-Alkoxyrest und Trifluormethylrest ausgewählten Rest bedeutet;

n eine ganze Zahl ist und den Wert von 0 bis einschließlich 2 hat;

Q eine Gruppe CH oder N ist; und

L einen C_1—C_6-Alkylrest bedeutet, der gegebenenfalls mit höchstens 3 Resten substituiert ist, die jeweils und unabhängig voneinander aus der Gruppe Halogenatom, Cyangruppe, Hydroxylgruppe, Isothiocyanatgruppe, C_1—C_6-Alkoxyrest, Arylrest, Aryloxyrest, Arylthiorest, Arylsulfonylrest und Aminogruppe ausgewählt ist; einen C_3—C_6-Alkenylrest; Aryl-C_3—C_6-alkenylrest; C_3—C_6-Cycloalkylrest, der gegebenenfalls mit einer Cyangruppe und/oder Arylgruppe substituiert ist; einen 1-(Aryl-C_2—C_6-alkyl)-1H-benzimidazol-2-ylrest oder einen Rest der allgemeinen Formel Z—C_mH_{2m}— bedeutet, wobei in der allgemeinen Formel

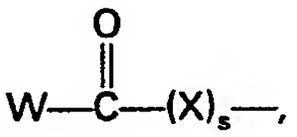
m eine ganze Zahl ist und den Wert 1 bis einschließlich 6 hat; und

Z die folgende Bedeutung hat: einen Rest aus der Gruppe 4,5-Dihydro-5-oxo-1H-tetrazol-1-ylrest, der gegebenenfalls in der 4-Stellung mit einem Arylrest oder einem C_1—C_6-Alkylrest substituiert ist; 2,3-Dihydro-1,4-benzodioxin-2-ylrest; 2,3-Dihydro-1,4-benzodioxin-6-ylrest; 2,3-Dihydro-2-oxo-1H-benzimidazol-1-ylrest; 2,3-Dihydro-3-oxo-4H-benzoxazin-4-ylrest; (10,11-Dihydro-5H-dibenzo-[a,d]-cyclohepten-5-yliden]-methylrest; 4-Morpholinylrest, 1-Piperidinylrest; 1-Pyrrolidinylrest und ein Rest der allgemeinen Formel T—N(R^4)—, wobei in der allgemeinen Formel

R^4 ein Wasserstoffatom, einen C_1—C_6-Alkylrest oder Aryl-C_1—C_6-alkylrest bedeutet und

T einen C_1—C_6-Alkylrest, Arylrest, Aryl-C_1—C_6-alkylrest oder einen 1H-Benzimidazol-2-ylrest bedeutet; und

ein Rest der allgemeinen Formel



wobei in der allgemeinen Formel

s 0 oder 1 ist;

X einen Rest O oder —N(R^5)— ist, wobei R^5 ein Wasserstoffatom, einen C_1—C_6-Alkylrest, Aryl-C_1—C_6-alkylrest, C_1—C_6-Alkanoylrest oder einen Aroylrest bedeutet; and

W einen C_1—C_6-Alkylrest, Arylrest, Aryl-C_1—C_6-alkylrest, Amino-, Arylaminogruppe, Mono- und Di-(C_1—C_6-alkyl)-aminogruppe, Mono- und Di-(aryl-C_1—C_6-alkyl)-aminogruppe, einen 1-Piperidinyl- 1-Pyrrolidinyl- oder 4-Morpholinylrest darstellt;

wobei der in den vorstehenden Definitionen verwendete Ausdruck Aryl- einen Rest kennzeichnet, aus der Gruppe Phenylrest, substituierter Phenylrest, Naphthalenylrest, Thienylrest, Halogenthienylrest, (C_1—C_6-Alkyl)-thienylrest, Pyridinylrest, Mono- und Di-(C_1—C_6-Alkyloxy)-pyridinylrest, Furanylrest und 1-(C_1—C_6-Alkyl)-pyrrolylrest; wobei der erwähnte Substituent Phenylrest eine Phenylgruppe bedeutet, die 1 bis 3 Substituenten hat, die jeweils und unabhängig voneinander aus der nachstehenden Gruppe ausgewählt sind: Halogenatom, Hydroxylgruppe, Nitrogruppe, Cyangruppe, Trifluor-

methylgruppe, C_1—C_6-Alkylrest, C_1—C_6-Alkylthiorest, C_1—C_6-Alkylsulfonylrest, C_1—C_6-Alkylsulfonyl-C_1—C_6-alkylrest, Phenyl-C_1—C_6-alkylsulfonylrest, Phenylsulfonyl-C_1—C_6-alkylrest, Aminogruppe, Mono- und Di-(C_1—C_6-alkyl)-aminogruppe, C_1—C_6-Alkanoylrest und ein Rest der allgemeinen Formel R^6—C_pH_{2p}—O—, in der

p eine ganze Zahl ist und den Wert 1 bis einschließlich 6 hat; und

R^6 einen Rest aus der nachstehenden Gruppe bedeutet: Wasserstoffatom, Aminogruppe, Cyangruppe, Phenylgruppe, Aminocarbonylrest, Mono- und Di-(C_1—C_6-alkyl)-aminocarbonylrest, C_1—C_6-Alkyloxycarbonylrest, Phenyl-C_1—C_6-alkyloxycarbonylrest, 4-Morpholinylcarbonylrest, 1-Piperidinylcarbonylrest und 1-Pyrrolidinylcarbonylrest, C_3—C_6-Alkenylrest, und ein Rest der allgemeinen Formel R^7—O— in der

R^7 einen C_1—C_6-Alkanoylrest, Phenylcarbonylrest, Phenyl-C_1—C_6-alkylcarbonylrest, C_1—C_6-Alkyloxycarbonylrest, Phenyl-C_1—C_6-alkyloxycarbonylrest, Aminocarbonylrest, Phenylaminocarbonylrest, Mono- oder Di-(C_1—C_6-alkyl)aminocarbonylrest bedeutet,

wobei der Ausdruck Phenylrest in der Definition des Restes R^7 einen gegebenenfalls mit bis zu 3 Resten substituierten Phenylrest bedeutet, die jeweils und unabhängig voneinander aus der nachstehenden Gruppe ausgewählt sind: Halogenatom, Cyangruppe, Nitrogruppe, C_1—C_6-Alkylrest und C_1—C_6-Alkoxyrest;

und wobei der Ausdruck Aroylrest bei der Definition von X einen Arylcarbonylrest bedeutet, bei dem die Arylgruppe die vorstehende Bedeutung hat.

2. Chemische Verbindung aus der Gruppe 1 - (4 - Fluorphenylmethyl) - N - [1 - [2 - (4 - methoxyphenyl) - äthyl] - 4 - piperidinyl] - 1H - benzimidazol - 2 - amin und ihre pharmazeutisch verträglichen Säureadditionssalze.

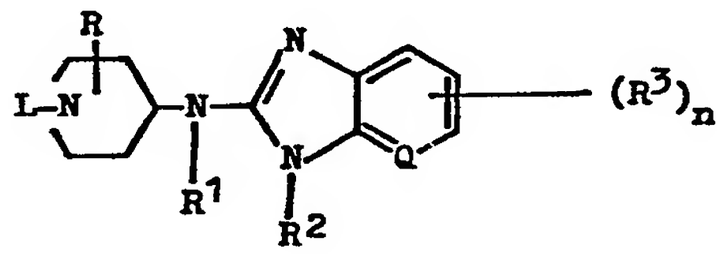
3. Chemische Verbindung aus der Gruppe 4 - [2 - [4 - [1 - (4 - Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenol und ihre pharmazeutisch verträglichen Säureadditionssalze.

4. Chemische Verbindung aus der Gruppe [4 - [2 - [4 - [1 - (4 - Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenyl] - benzolacetat sowie ihre pharmazeutisch verträglichen Säureadditionssalze.

5. Chemische Verbindung aus der Gruppe [4 - [2 - [4 - [1 - (4 - Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenoxy] - acetonitril und ihre pharmazeutisch verträglichen Säureadditionssalze.

6. Chemische Verbindung aus der Gruppe N - [1 - (2 - Phenyläthyl) - 4 - piperidinyl] - 1 - (phenylmethyl) - 1H - benzimidazol - 2 - amin und ihre pharmazeutisch verträglichen Säureadditionssalze.

7. Pharmazeutische Zubereitung mit antihistaminischer Wirksamkeit, enthaltend ein inertes Trägermaterial und als aktiven Bestandteil eine antihistaminisch wirksame Menge einer chemischen Verbindung aus der Gruppe der N-Heterocyclyl-4-piperidinamine der allgemeinen Formel

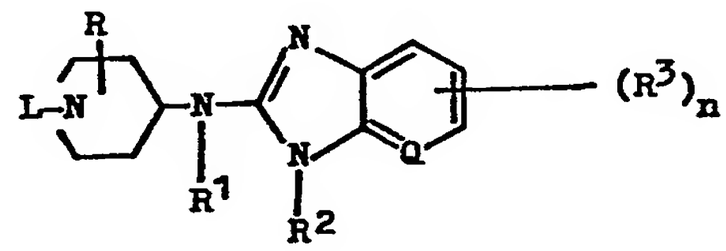


(I)

gemäß Anspruch 1 sowie ihre pharmazeutisch wirksamen Säureadditionssalze.

8. Pharmazeutische Zubereitung mit antihistaminischer Wirksamkeit, enthaltend ein inertes Trägermaterial und als aktiven Bestandteil eine antihistaminisch wirksame Menge einer Verbindung gemäß jedem der Ansprüche 2 bis 6.

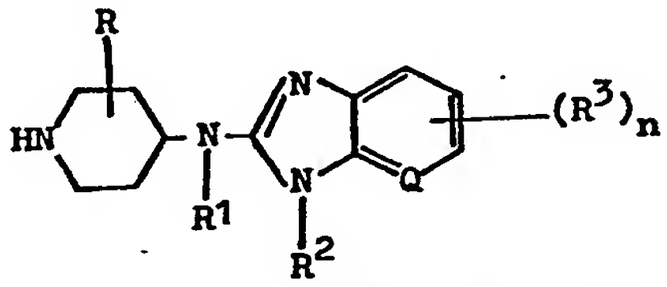
9. Verfahren zur Herstellung einer chemischen Verbindung aus der Gruppe der N-Heterocyclyl-4-piperidinamine der allgemeinen Formel



(I)

sowie ihrer pharmazeutisch verträglichen Säureadditionsalze, wobei in der allgemeinen Formel die Reste L, R, R^1, R^2, R^3, Q und n die in Anspruch 1 angegebene Bedeutung haben, dadurch gekennzeichnet, daß man

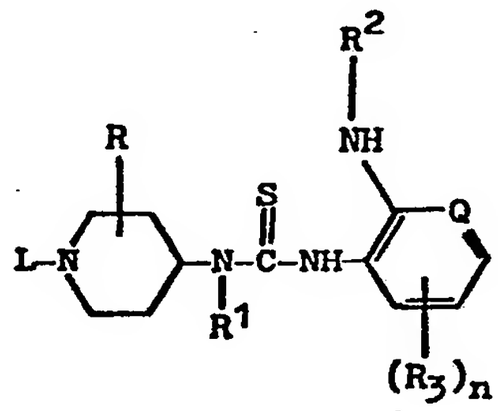
(a) bei einer Ausgangsverbindung der allgemeinen Formel



(II)

in der die Reste R, R^1, R^2, R^3, n und Q die vorstehende Bedeutung haben, den erwünschten L-Substituenten am Piperidinstickstoff in an sich bekannter Weise einführt;

(b) oder die Verbindungen der Formel I durch Cyclodesulfurierung eines geeigneten Thioharnstoffderivates der Formel



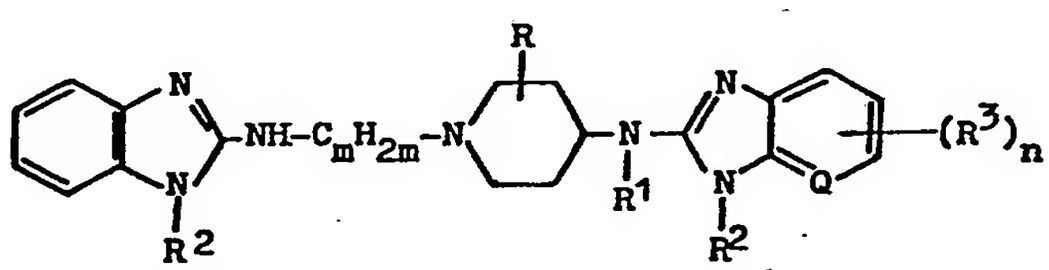
(V)

bewerkstelligt, oder

(c) zur Herstellung der Verbindung der Formel (I), in der R^2 kein Wasserstoffatom bedeutet, der Rest R^2 mit dem Symbol R^2_a gekennzeichnet ist und die herzustellenden Verbindungen mit der Formel (I-a), wobei man von einer entsprechenden Verbindung (I) ausgeht, in der R^2 ein Wasserstoffatom bedeutet, (I-b), und man den erwähnten Rest R^2_a in an sich bekannter Weise einführt; oder

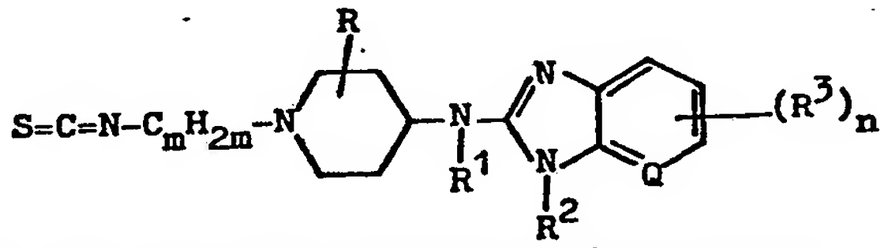
(d) zur Herstellung von Verbindungen (I), in denen R^1 und R^2 beide kein Wasserstoffatom bedeuten, der Rest R^1 mit dem Symbol R^1_a und der Rest R^2 mit dem Symbol R^2_a gekennzeichnet ist, in den entsprechenden Verbindungen, in denen R^1 ein Wasserstoffatom bedeutet, die R^1_a-Gruppe gemäß der vorstehend beschriebenen Verfahrensstufe (c) für die Herstellung der Verbindung (I-b) ausgehend von (I-a) einführt; oder

(e) zur Herstellung einer Verbindung der allgemeinen Formel (I-c)



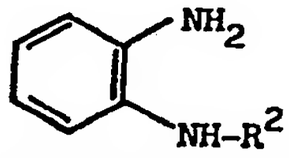
(I-c)

ein Isothiocyanat der Formel (VII)



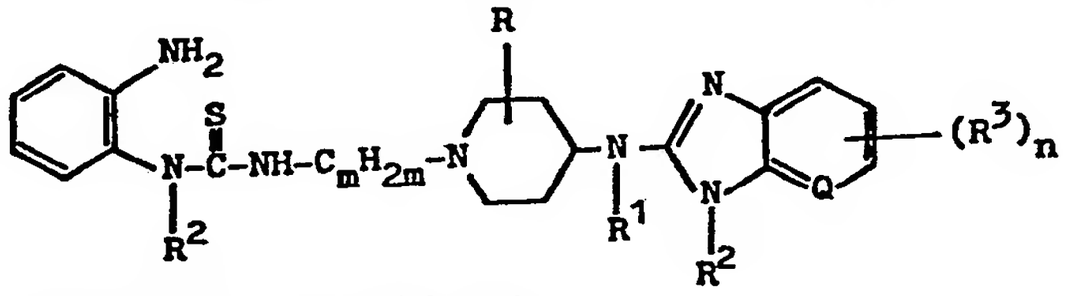
(VII)

einer Additionsreaktion mit einem Benzoldiamin der Formel (VIII)



(VIII)

unterwirft, und anschließend das gebildete Thioharnstoff-Zwischenprodukt der Formel (IX)



(IX)

einer Cyclodesulfurierungsreaktion unterwirft; oder

(f) zur Herstellung von Verbindungen der Formel (I), in der L den Rest $Z—C_mH_{2m}—$ bedeutet, in

dem Z einen Rest der Formel W—CO—$(X)_s$— darstellt, wobei s 1 ist, X gleich O ist und W einen gegebenenfalls substituierten Aminrest, einen 1-Pyrrolidinylrest, 4-Morpholinylrest oder 1-Piperidinylrest darstellt, wobei die letztgenannten Verbindungen durch die allgemeine Formel (I-d) gekennzeichnet sind, das entsprechende Amin-, Pyrrolidin-, Morpholin- oder Piperidin-Derivat mit einem geeigneten N-[1-(halogen-C_1—C_6-alkyl)-4-piperidinyl]-1H-benzimidazol-2-aminderivat in Gegenwart eines geeigneten Carbonats umsetzt; oder

(g) zur Herstellung von Verbindungen der allgemeinen Formel (I), die mindestens eine Hydroxylgruppe als Substituent enthalten, ausgehend von den entsprechenden phenylmethoxysubstituierten Verbindungen die letztgenannten Verbindungen einer katalytischen Hydrierung in Gegenwart eines geeigneten Katalysators unterwirft, oder die genannten Hydroxylderivate aus den entsprechenden C_1—C_6-alkyloxysubstituierten Analoga mittels Hydrolyse der letztgenannten Verbindungen in saurem Medium gewinnt, wobei man beispielsweise Bromwasserstoffsäure in Salzsäure einsetzt, und, gewünschtenfalls, die hydroxylsubstituierten Verbindungen wiederum O-alkyliert oder O-acyliert, indem man die letztgenannten Verbindungen mit einem Halogenid, einem C_1—C_6-Alkanoylhalogenid, einem Alkyloxycarbonylhalogenid oder einem Isocyanat umsetzt, oder man die hydroxylsubstituierten Verbindungen durch Umsetzung mit einem geeigneten Halogenierungsmittel in die Halogenide umwandelt; oder

(h) aus den entsprechenden nitro- und cyan-substituierten Verbindungen durch Reduktion die entsprechenden amino-substituierten Verbindungen enthält, beispielsweise durch katalytische Hydrierung in Gegenwart eines geeigneten Katalysators und, gewünschtenfalls, die genannten amino-substituierten Verbindungen wiederum durch Umsetzung mit einem geeigneten Alkylierungs- oder Acylierungsmittel N-alkyliert oder N-acyliert; oder

(i) zur Herstellung von sec.- oder tert.-aminsubstituierten Verbindungen der Formel (I) beispielsweise eine geeignete halogensubstituierte Verbindung mit dem gewünschten primären oder sekundären Amin substituiert, oder

(j) zur Herstellung von aminocarbonyl-substituierten Verbindungen die entsprechenden Ester mit Ammoniak oder einem geeigneten primären oder sekundären Amin in einem geeigneten Lösungsmittel zur Umsetzung bringt; oder

(k) zur Herstellung von Verbindungen der Formel (I), die in ihrer Struktur eine Sulfonylgruppe enthalten, ausgehend aus den entsprechenden Thioverbindungen, diese mit einem geeigneten Oxidationsmittel oxidiert; und, gewünschtenfalls, die erhaltene Verbindung (I) in die Form ihrer pharmazeutisch wirksamen, nicht toxischen Säureadditionssalze durch Umsetzung mit einer entsprechenden Säure bringt, oder die Salze durch Behandlung mit Alkali in die freie Basenform umwandelt.

10. Verfahren zur Herstellung einer chemischen Verbindung aus der Gruppe 1 - (4 - Fluorphenylmethyl) - N - [1 - [2 - (4 - methoxyphenyl) - äthyl] - 4 - piperidinyl] - 1H - benzimidazol - 2 - amin und ihrer pharmazeutisch verträglichen Säureadditionssalze, dadurch gekennzeichnet, daß man 1 - [(4-Fluorphenyl)methyl] - N - (4 - piperidinyl) - 1H - benzimidazol - 2 - amin - dihydrobromid mit 2 - (4-Methoxyphenyl) - äthylmethansulfonat umsetzt.

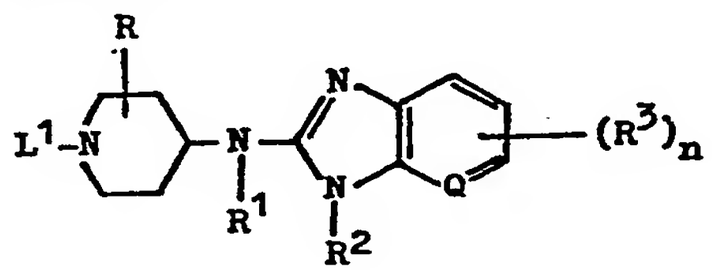
11. Verfahren zur Herstellung einer chemischen Verbindung aus der Gruppe 4 - [2 - [4 - [1 - (4-Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenol und ihrer pharmazeutisch verträglichen Säureadditionssalze, dadurch gekennzeichnet, daß man 1 - (4 - Fluorphenylmethyl) - N - [1 - [2 - [4 - (phenylmethoxy) - phenyl] - äthyl] - 4 - piperidinyl] - 1H - benzimidazol-2 - amin hydriert.

12. Verfahren zur Herstellung einer chemischen Verbindung aus der Gruppe [4 - [2 - [4 - [1 - (4-Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenyl] - benzolacetat und ihrer pharmazeutisch verträglichen Säureadditionssalze, dadurch gekennzeichnet, daß man 4-[2 - [4 - [1 - (4 - Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenol mit Benzolacetylchlorid umsetzt.

13. Verfahren zur Herstellung einer chemischen Verbindung aus der Gruppe [4 - [2- [4 - [1 - (4-Fluorphenylmethyl) - 1H - benzimidazol - 2 - ylamino] - 1 - piperidinyl] - äthyl] - phenoxy] - acetonitril und ihrer pharmazeutisch verträglichen Säreadditionssalze, dadurch gekennzeichnet, daß man 4 - [2 - [4 - [1 - (4 - Fluorphenylmethyl) - 1H - benzimidazol - 2 -ylamino] - 1 - piperidinyl] - äthyl]-phenol mit Chloracetonitril umsetzt.

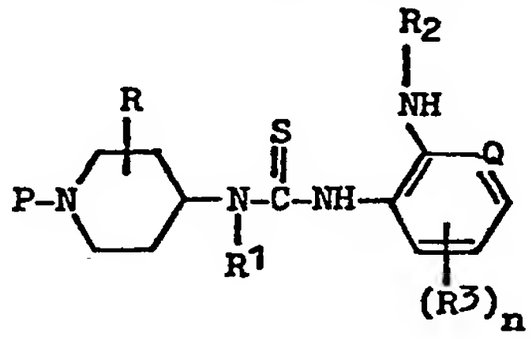
14. Verfahren zur Herstellung von N - [1 - (2 - Phenyläthyl) - 4 - piperidinyl] - 1 - (phenylmethyl) - 1H - benzimidazol - 2 - amin, dadurch gekennzeichnet, daß man 1 - (Phenylmethyl) - N-(4 - piperidinyl) - 1H - benzimidazol - 2 - amin - dihydrobromid mit (2 - Bromäthyl) - benzol umsetzt.

15. Chemische Verbindung der Formel



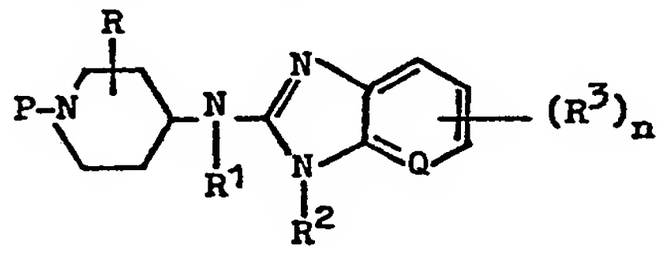
in der L^1 einen C_1—C_6-Alkyloxycarbonylrest oder Phenylmethoxycarbonylrest bedeutet und die Reste R, R^1, R^2, R^3, Q und n die in Anspruch 1 angegebene Bedeutung haben.

16. Verfahren zur Herstellung einer chemischen Verbindung nach Anspruch 15, dadurch gekennzeichnet, daß man in an sich bekannter Weise eine Verbindung der allgemeinen Formel (X)



(X)

cyclodesulfuriert, um eine Verbindung der allgemeinen Formel (XI) zu erhalten



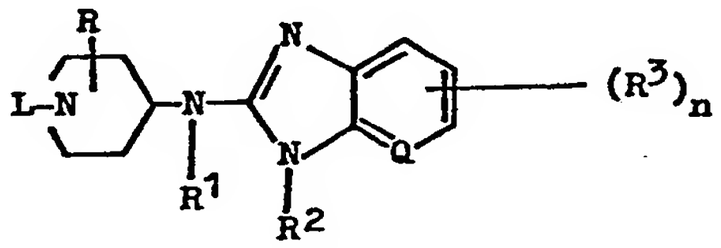
(XI)

in der P einen C_1—C_6-Alkoxycarbonyl- oder Phenylmethoxycarbonylrest bedeutet, und man gewünschtenfalls den genannten Rest P zur Herstellung einer Verbindung, in der L^1 ein Wasserstoffatom bedeutet, abspaltet, wobei, sofern der Rest P einen C_1—C_6-Alkoxycarbonylrest bedeutet, die Abspaltung mittels alkalischer oder saurer Hydrolyse erfolgen kann, beispielsweise unter Verwendung von Bromwasserstoffsäure in Eisessig, und man, sofern die genannte Schutzgruppe einen Phenylmethoxycarbonylrest darstellt, diesen durch alkalische oder saure Hydrolyse abspalten kann, oder durch katalytische Hydrierung unter Verwendung eines geeigneten Katalysators, wie Palladium-auf-Holzkohle.

17. Verwendung einer Verbindung nach jedem der Ansprüche 1 bis 6 oder einer Zubereitung gemäß Anspruch 7 oder 8 als Antihistaminikum.

Revendications

1. Composé chimique, choisi dans le groupe consistant en une N-hétérocyclyl-4-pipéridinamine ayant pour formule:



(I)

et les sels d'addition d'acides acceptables en pharmacie, où:

R est un élément choisi dans le groupe consistant en hydrogène et alcoyle C_1—C_6;

R^1 est un élément choisi dans le groupe consistant en hydrogène, alcoyle C_1—C_6, cycloalcoyle C_1—C_6, aryl-alcoyle C_1—C_6 et alcanoyle C_1—C_6;

R^2 est un élément choisi dans le groupe consistant en hydrogène, alcoyle ayant de 1 à 10 atomes de carbone, aryle, cycloalcoyle C_3—C_6 et mono- et diaryl(alcoyle C_1—C_6);

R^3 est un élément indépendamment choisi dans le groupe consistant en halo, alcoyle C_1—C_6, alcoyloxy C_1—C_6 et trifluorométhyle;

n est un nombre entier de 0 à 2 inclus;

Q est un élément choisi dans le groupe consistant en CH et N; et

L est un élément choisi dans le groupe consistant en alcoyle C_1—C_6, ayant éventuellement jusqu'à 3 substituants, chacun étant indépendamment choisi dans le groupe consistant en halo, cyano, hydroxy, isothiocyanato, alcoyloxy C_1—C_6, aryle, aryloxy, arylthio, arylsulfonyle, amino; alkényle C_3—C_6; aryl-alkényle C_3—C_6; cycloalcoyle C_3—C_6, éventuellement substitué par un groupement cyano et/ou aryle; 1-(aryl-alcoyle C_1—C_6)-1H-benzimidazol-2-yl; et un radical de formule Z—C_mH_{2m}—, où

m est un nombre entier de 1 à 6 inclus; et

Z est un élément choisi dans le groupe consistant en 4,5-dihydro-5-oxo-1H-tétrazol-1-yl, éventuellement substitué en position 4 par un radical aryle ou un radical alcoyle C_1—C_6; 2,3-dihydro-1,4-benzodioxine-2-yl; 2,3-dihydro-1,4-benzodioxine-6-yl; 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl; 2,3-dihydro-3-oxo-4H-benzoxazine-4-yl; (10,11-dihydro-5H-dibenzo[a,d]cycloheptène-5-ylidène méthyle; 4-morpholinyle; 1-pipéridinyle; 1-pyrrolidinyle; un radical de formule T—N(R^4)—, dans lequel

R^4 est un élément choisi dans le groupe consistant en hydrogène, alcoyle C_1—C_6 et aryl-alcoyle C_1—C_6; et

T est un élément choisi dans le groupe consistant en alcoyle C_1—C_6, aryle, aryl-alcoyle C_1—C_6, 1H-benzimidazol-2-yl; et

un radical de formule

$$W—\overset{\overset{O}{\|}}{C}—(X)_s—, \text{ où}$$

s est le nombre entier 0 ou 1;

X est un élément choisi dans le groupe consistant en O et —$N(R^5)$—, R^5 étant un élément choisi dans le groupe consistant en hydrogène, alcoyle C_1—C_6, aryl-alcoyle C_1—C_6, alcanoyle C_1—C_6 et aroyle; et

W est un élément choisi dans le groupe consistant en alcoyle C_1—C_6, aryle, aryl (alcoyle C_1—C_6), amino, arylamino, mono- et di-alcoyle C_1—C_6) amino, mono- et di(aryl-alcoyle C_1—C_6)amino, 1-pipéridinyle, 1-pyrrolidinyle et 4-morpholinyle;

l'aryle, dans les définitions qui précèdent, étant un élément choisi dans le groupe consistant en phényle, phényle substitué, naphtalényle, thiényle, halothiényle, (alcoyle C_1—C_6) thiényle, pyridinyle, mono- et di(alcoyloxy C_1—C_6)pyridinyle, furanyle et 1-(alcoyle C_1—C_6)pyrrolyle; ledit phényle substitué étant un phényle ayant de 1 à 3 substituants chacun étant indépendamment choisi dans le groupe consistant en halo, hydroxy, nitro, cyano, trifluorométhyle, alcoyle C_1—C_6, (alcoyle C_1—C_6) thio, (alcoyle C_1—C_6)sulfonyle, (alcoyle C_1—C_6)sulfonyl (alcoyle C_1—C_6), phényl(alcoyle C_1—C_6)sulfonyle, phénylsulfonyl (alcoyle C_1—C_6), amino, mono- et di (alcoyle C_1—C_6)amino, alcanoyle C_1—C_6, un radical de formule R^6—C_pH_{2p}—O—, où

p est un nombre entier de 1 à 6 inclus; et

R^6 est un élément choisi dans le groupe consistant en hydrogène, amino, cyano, phényle, aminocarbonyle, mono- et di(alcoyle C_1—C_6)aminocarbonyle, alcoyle C_1—C_6-oxycarbonyle, phényl(alcoyloxy C_1—C_6) carbonyle, 4-morpholinylcarbonyle, 1-pipéridinylcarbonyle et 1-pyrrolidinylcarbonyle, alkényle C_3—C_6 et un radical de formule R^7 —O—, où

R^7 est un élément choisi dans le groupe consistant en alcanoyle C_1—C_6, phénylcarbonyle, phényl (alcoyle C_1—C_6) carbonyle, (alcoyloxy C_1—C_6)carbonyle, phényl(alcoyloxy C_1—C_6)carbonyle, aminocarbonyle, phénylaminocarbonyle, mono- et di (alcoyle C_1—C_6)aminocarbonyle,

ledit phényle dans la définition de R^7 pouvant éventuellement avoir jusqu'à 3 substituants chacun étant indépendamment choisi dans le groupe consistant en halo, cyano, nitro, alcoyle C_1—C_6 et alcoyloxy C_1—C_6; et ledit aryle dans la définition de L représente un arylcarbonyle;

ledit aryle étant tel que défini ci-dessus.

2. Composé chimique choisi dans le groupe consistant en 1 - (4 - fluorophénylméthyl) - N-{1 - [2 - (4 - méthoxyphényl)éthyl] - 4 - pipéridinyl} - 1H - benzimidazol - 2 - amine et ses sels d'addition d'acides acceptables en pharmacie.

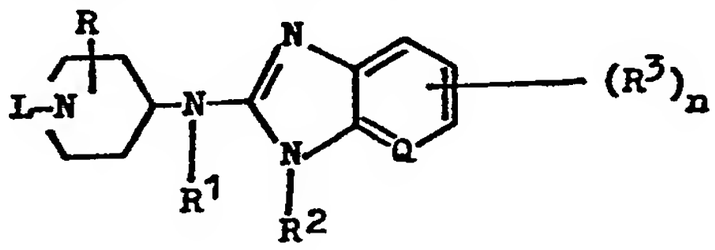
3. Composé chimique choisi dans le groupe consistant en 4 - [2 - {4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl} - éthyl]phénol et ses sels d'addition d'acides acceptables en pharmacie.

4. Composé chimique choisi dans le groupe consistant en {4 - [2 - {4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}éthyl]phényl}benzèneacétate et ses sels d'addition d'acides acceptables en pharmacie.

5. Composé chimique choisi dans le groupe consistant en {4 - [2 - {4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}éthyl]phénoxy}acétonitrile et ses sels d'addition d'acides acceptables en pharmacie.

6. Composé chimique choisi dans le groupe consistant en N - [1 - (2(phényléthyl) 4 - pipéridinyl] - 1 - (phénylméthyl) - 1H - benzimidazol - 2 - amine et ses sels d'addition d'acides acceptables en pharmacie.

7. Composition pharmaceutique antihistaminique comprenant un véhicule inerte et comme ingrédient actif, une quantité antihistaminique efficace d'un composé chimique choisi dans le groupe consistant en une N-hétérocyclyl-4-pipéridinamine ayant pour formule

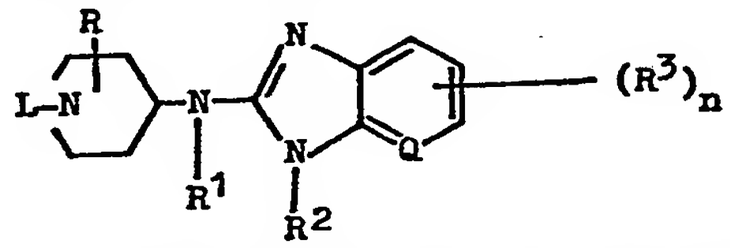


(I)

'selon la revendication 1 et ses sels d'addition d'acides acceptables en pharmacie.

8. Composition pharmaceutique antihistaminique comprenant un véhicule inerte et comme ingrédient actif, une quantité antihistaminique efficace d'un composé selon l'une quelconque des revendications 2 à 6.

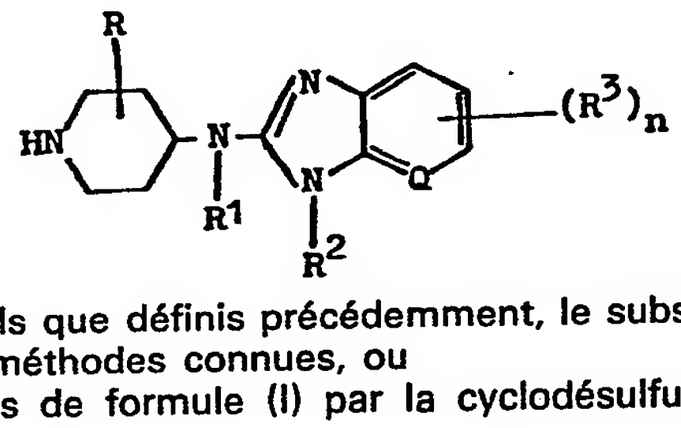
9. Procédé de préparation d'un composé chimique choisi dans le groupe consistant en une N-hétérocyclyl-4-pipéridinamine ayant pour formule



(I)

et ses sels d'addition d'acides acceptables en pharmacie, où L, R, R^1, R^2, R^3, Q et n sont tels que définis à la revendication 1, caractérisé en ce qu'il consiste à:

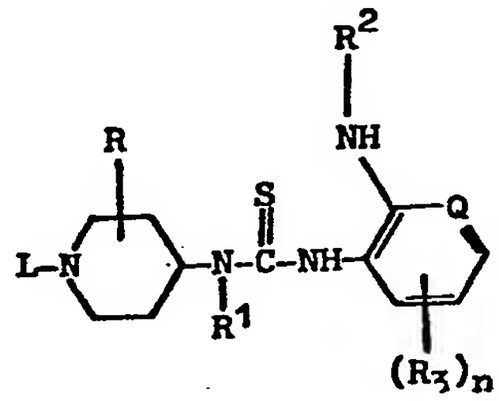
a) introduire, sur une matière première de formule:



(II)

où R, R^1, R^2, R^3, n et Q sont tels que définis précédemment, le substituant L souhaité sur l'azote de pipéridine par l'application de méthodes connues, ou

b) préparer des composés de formule (I) par la cyclodésulfuration d'un dérivé approprié de thiourée de formule



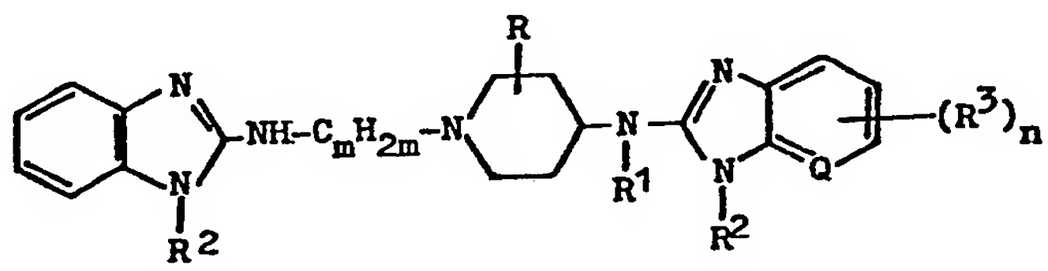
(V)

ou

c) préparer des composés de formule (I) où R^2 est autre que de l'hydrogène, ledit R^2 étant représenté par R^2_a et lesdits composés par le formule (I-a), en partant d'un composé (I) correspondant où R^2 est de l'hydrogène, (I-b), en introduisant ledit R^2_a selon des procédures connues; ou

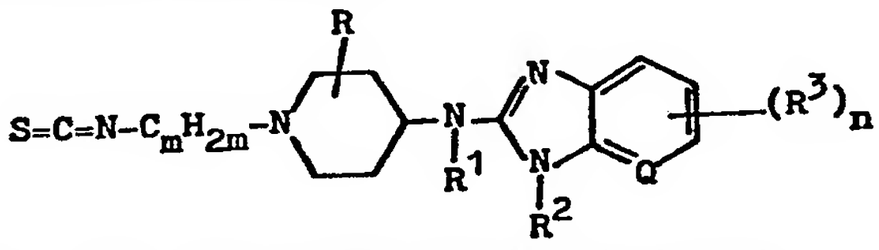
d) préparer des composés de formule (I) où R^1 et R^2 sont tous deux différents de l'hydrogène, ledit R^1 étant représenté par R^1_a et ledit R^2 par R^2_a, à partir des composés correspondants où R^1 est de l'hydrogène en introduisant le groupe R^1_a d'une façon semblable à ce qui a été décrit ci-dessus à l'étape c) pour la préparation du composé (I-b) en partant de (I-a); ou

e) préparer un composé de formule



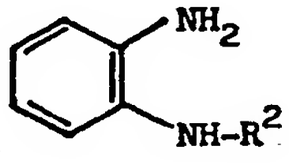
(I-c)

en soumettant un isothiocyanate de formule



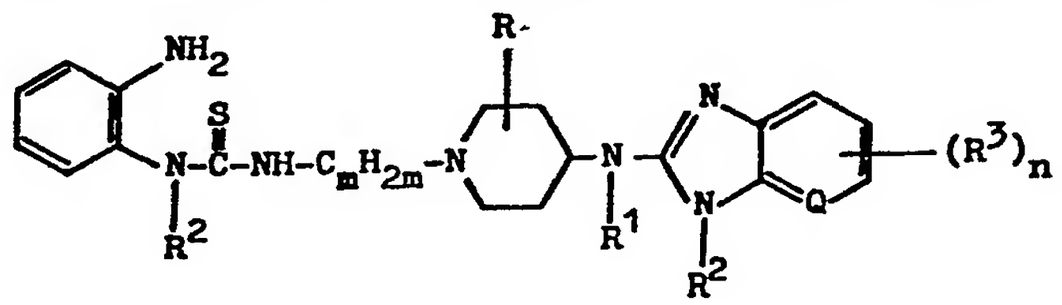
(VII)

à une réaction d'addition avec une benzène diamine de formule



(VIII)

et en cyclodésulfurant subséquemment la thiourée intermédiaire formée de formule



(IX)

ou

f) préparer des composés de formule (I) où L représente un radical Z—C_mH_{2m}—, où Z représente un radical de formule W—CO—$(X)_s$—, où s est 1, X est O et W est une amine éventuellement substituée, un 1-pyrrolidinyle, un 4-morpholinyle ou un 1-pipéridinyle, lesdits composés étant représentés par la formule (I-d), par réaction de l'amine, de la pyrrolidine, de la morpholine ou de la pipéridine correspondante avec une N-[1-(halo-alcoyle C_1—C_6)-4-pipéridinyl]-1H-benzimidazol-2-amine appropriée en présence d'un carbonate approprié; ou

g) préparer des composés de formule (I) contenant au moins un groupement hydroxyle comme substituant, à partir des composés correspondants substitués en phénylméthoxy en soumettant lesdits composés à une hydrogénation catalytique en présence d'un catalyseur approprié, ou en dérivant lesdits dérivés d'hydroxyle des analogues substitués en alcoyloxy C_1—C_6 en hydrolisant lesdits analogues dans un milieu acide, en utilisant par exemple du bromure d'hydrogène dans de l'acide acétique et, si on le souhaite, lesdits composés substitués en hydroxyle peuvent à leur tour être O-alcoylés ou acylés en les faisant réagir avec un halogénure, un halogénure d'alcanoyle C_1—C_6, un halogénure d'alcoyloxycarbonyle, ou un isocyanate ou lesdits composés substitués en hydroxyle peuvent également être convertis en halogénures en faisant réagir avec eux un agent halogénant approprié; ou

h) dériver de composés amino-substitués des composés nitro- et cyano-substitués correspondants par réduction de ces derniers, par exemple par hydrogénation catalytique en présence d'un catalyseur approprié et, si on le souhaite, lesdits composés amino-substitués peuvent à leur tour être N-alcoylés ou acylés par la réaction avec un agent alcoylant ou un agent acylant approprié; ou

i) préparer des composés substitués en amine secondaire ou tertiaire de formule (I) en remplaçant, par exemple, un composé halo-substitué approprié par l'amine primaire ou secondaire souhaitée; ou

j) dériver des composés substitués en aminocarbonyle des esters correspondants par réaction de ces derniers avec de l'ammoniac ou une amine primaire ou secondaire appropriée dans un solvant adapté; ou

k) dériver les composés de formule (I) contenant dans leur structure ou groupement sulfonyle, des composés thio correspondants en oxydant ces derniers avec un agent oxydant approprié; et si on le souhaite, convertir les composés de formule (I) en leur forme de sel d'addition d'acide non toxique thérapeutiquement actif par traitement avec un acide approprié, ou bien la forme de sel peut être convertie en une forme de base libre par traitement avec un alcali.

10. Procédé de préparation d'un composé chimique choisi dans le groupe consistant en 1 - (4-fluorophénylméthyl) - N - {1 - [2 - (4 - méthoxyphényl)éthyl] - 4 - pipéridinyl} -1H - benzimidazol - 2-amine et ses sels d'addition d'acides acceptables en pharmacie, caractérisé en ce qu'on fait réagir un dibromhydrate de 1 - [(4 - fluorophényl)méthyl] - N - (4 - pipéridinyl) - 1H - benzimidazol - 2 - amine avec du 2 - (4 - méthoxyphényl)éthylméthanesulfonate.

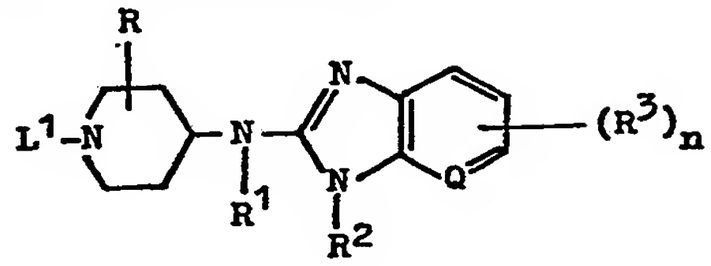
11. Procédé de préparation d'un composé chimique choisi dans le groupe consistant en 4 - [2-{4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}éthyl]phénol et ses sels d'addition d'acides acceptables en pharmacie, caractérisé par l'hydrogénation de 1 - (4 - fluorophénylméthyl) - N - [1 - {2 - [4 - (phénylméthoxy)phényl]éthyl} - 4 - pipéridinyl] - 1H - benzimidazol - 2-amine.

12. Procédé de préparation d'un composé chimique choisi dans le groupe consistant en {4 - [2-{4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}éthyl]phényl}benzène - acétate et ses sels d'addition d'acides acceptables en pharmacie, caractérisé en ce qu'on fait réagir du 4 - [2 - {4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}-éthyl] - phénol avec du chlorure de benzeneacétyle.

13. Procédé de préparation d'un composé chimique choisi dans le groupe consistant en {4 - [2-{4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}éthyl]phénoxy}-acétonitrile et ses sels d'addition d'acides acceptables en pharmacie, caractérisé en ce qu'on fait réagir un 4 - [2 - {4 - [1 - (4 - fluorophénylméthyl) - 1H - benzimidazol - 2 - ylamino] - 1 - pipéridinyl}-éthyl]phénol avec du chloroacétonitrile.

14. Procédé de préparation d'une N - [1 - (2 - phényléthyl) - 4 - pipéridinyl] - 1 - (phénylméthyl) - 1H - benzimidazol - 2 - amine, caractérisé en ce qu'on fait réagir un dibromhydrate de 1 - (phénylméthyl) - N - (4 - pipéridinyl) - 1H - benzimidazol - 2 - amine avec du (2 - bromoéthyl)-benzène.

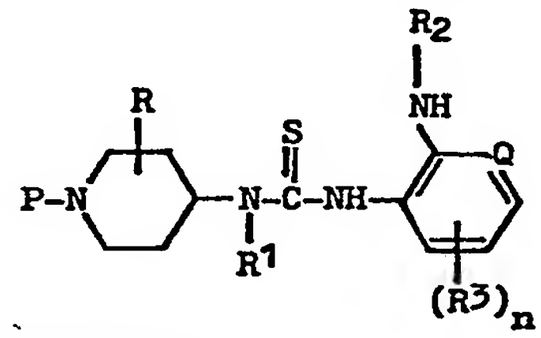
15. Composé chimique, ayant pour formule:



où

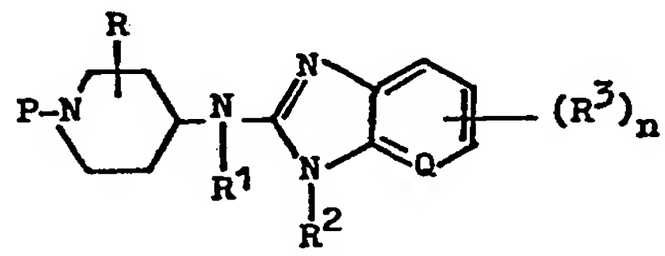
L^1 est un élément choisi dans le groupe consistant en hydrogène, alcoyloxy C_1—C_6-carbonyle et phénylméthoxycarbonyle; et R, R^1, R^2, R^3, Q et n sont tels que définis à la revendication 1.

16. Procédé de préparation d'un composé chimique selon la revendication 15, caractérisé par la cyclodésulfuration, par des méthodes connues, d'un composé de formule



(X)

afin de préparer un composé de formule



(XI)

où P est un alcoxy C_1—C_6-carbonyle, ou un phénylméthoxycarbonyle et, si on le souhaite, l'élimination dudit groupe P afin de préparer le composé où L' est de l'hydrogène, quand ledit groupe P est un alcoyloxy C_1—C_6-carbonyle, il peut être enlevé par un hydrolyse alcaline ou acide en utilisant, par exemple, de l'acide bromhydrique dans de l'acide acétique glacial, et quand ledit groupe protecteur est un groupe phénylméthoxycarbonyle, il peut être enlevé par hydrolyse alcaline ou acide ou par hydrogénation catalytique en utilisant un catalyseur approprié tel que du palladium sur charbon de bois.

17. Composé selon l'une quelconque des revendications 1 à 6 ou composition selon la revendication 7 ou la revendication 8 à utiliser comme agent antihistaminique.